Vaccines for preventing rotavirus diarrhoea: vaccines in use (Review)

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[Intervention Review]

Vaccines for preventing rotavirus diarrhoea: vaccines in use

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ABSTRACT

Background

Rotavirus results in more diarrhoea-related deaths in children less than five years of age than any other single agent in countries with high childhood mortality. It is also a common cause of diarrhoea-related hospital admissions in countries with low childhood mortality. Currently licensed rotavirus vaccines include a monovalent rotavirus vaccine (RV1; Rotarix, GlaxoSmithKline Biologicals) and a pentavalent rotavirus vaccine (RV5; RotaTeq, Merck & Co., Inc.). Lanzhou lamb rotavirus vaccine (LLR; Lanzhou Institute of Biomedical Products) is used in China only.

Objectives

To evaluate rotavirus vaccines approved for use (RV1, RV5, and LLR) for preventing rotavirus diarrhoea.

Search methods

We searched MEDLINE (via PubMed) (1966 to May 2012), the Cochrane Infectious Diseases Group Specialized Register (10 May 2012), CENTRAL (published in *The Cochrane Library* 2012, Issue 5), EMBASE (1974 to 10 May 2012), LILACS (1982 to 10 May 2012), and BIOSIS (1926 to 10 May 2012). We also searched the ICTRP (10 May 2012), www.ClinicalTrials.gov (28 May 2012) and checked reference lists of identified studies.

Selection criteria

We selected randomized controlled trials (RCTs) in children comparing rotavirus vaccines approved for use with placebo, no intervention, or another vaccine.

Data collection and analysis

Two authors independently assessed trial eligibility, extracted data, and assessed risk of bias. We combined dichotomous data using the risk ratio (RR) and 95% confidence intervals (CI). We stratified the analysis by child mortality, and used GRADE to evaluate evidence quality.

Main results

Forty-one trials met the inclusion criteria and enrolled a total of 186,263 participants. Twenty-nine trials (101,671 participants) assessed RV1, and 12 trials (84,592 participants) evaluated RV5. We did not find any trials assessing LLR.

RV1

Children aged less than one year: In countries with low-mortality rates, RV1 prevents 86% of severe rotavirus diarrhoea cases (RR 0.14, 95% CI 0.07 to 0.26; 40,631 participants, six trials; high-quality evidence), and, based on one large multicentre trial in Latin America and Finland, probably prevents 40% of severe all-cause diarrhoea episodes (rate ratio 0.60, 95% CI 0.50 to 0.72; 17,867 participants, one trial; moderate-quality evidence). In countries with high-mortality rates, RV1 probably prevents 63% of severe rotavirus diarrhoea cases (RR 0.37, 95% CI 0.18 to 0.75; 5414 participants, two trials; moderate-quality evidence), and, based on one trial in Malawi and South Africa, 34% of severe all-cause diarrhoea cases (RR 0.66, 95% CI 0.44 to 0.98; 4939 participants, one trial; moderate-quality evidence).

Children aged up to two years: In countries with low-mortality rates, RV1 prevents 85% of severe rotavirus diarrhoea cases (RR 0.15, 95% CI 0.12 to 0.20; 32,854 participants, eight trials; high-quality evidence), and probably 37% of severe all-cause diarrhoea episodes (rate ratio 0.63, 95% CI 0.56 to 0.71; 39,091 participants, two trials; moderate-quality evidence). In countries with high-mortality rates, based on one trial in Malawi and South Africa, RV1 probably prevents 42% of severe rotavirus diarrhoea cases (RR 0.58, 95% CI 0.42 to 0.79; 2764 participants, one trial; moderate-quality evidence), and 18% of severe all-cause diarrhoea cases (RR 0.82, 95% CI 0.71 to 0.95; 2764 participants, one trial; moderate-quality evidence).

RV5

Children aged less than one year: In countries with low-mortality rates, RV5 probably prevents 87% of severe rotavirus diarrhoea cases (RR 0.13, 95% CI 0.04 to 0.45; 2344 participants, three trials; moderate-quality evidence), and, based on one trial in Finland, may prevent 72% of severe all-cause diarrhoea cases (RR 0.28, 95% CI 0.16 to 0.48; 1029 participants, one trial; low-quality evidence). In countries with high-mortality rates, RV5 prevents 57% of severe rotavirus diarrhoea (RR 0.43, 95% CI 0.29 to 0.62; 5916 participants, two trials; high-quality evidence), but there was insufficient data to assess the effect on severe all-cause diarrhoea.

Children aged up to two years: Four studies provided data for severe rotavirus and all-cause diarrhoea in countries with low-mortality rates. Three trials reported on severe rotavirus diarrhoea cases and found that RV5 probably prevents 82% (RR 0.18, 95% CI 0.07 to 0.50; 3190 participants, three trials; moderate-quality evidence), and another trial in Finland reported on severe all-cause diarrhoea cases and found that RV5 may prevent 96% (RR 0.04, 95% CI 0.00 to 0.70; 1029 participants, one trial; low-quality evidence). In high-mortality countries, RV5 prevents 41% of severe rotavirus diarrhoea cases (RR 0.59, 95% CI 0.43 to 0.82; 5885 participants, two trials; high-quality evidence), and 15% of severe all-cause diarrhoea cases (RR 0.85, 95% CI 0.75 to 0.98; 5977 participants, two trials; high-quality evidence).

There was no evidence of a vaccine effect on mortality (181,009 participants, 34 trials; low-quality evidence), although the trials were not powered to detect an effect on this end point.

Serious adverse events were reported in 4565 out of 99,438 children vaccinated with RV1 and in 1884 out of 78,226 children vaccinated with RV5. Fifty-eight cases of intussusception were reported in 97,246 children after RV1 vaccination, and 34 cases in 81,459 children after RV5 vaccination. No significant difference was found between children receiving RV1 or RV5 and placebo in the number of serious adverse events, and intussusception in particular.

Authors' conclusions

RV1 and RV5 prevent episodes of rotavirus diarrhoea. The vaccine efficacy is lower in high-mortality countries; however, due to the higher burden of disease, the absolute benefit is higher in these settings. No increased risk of serious adverse events including intussusception was detected, but post-introduction surveillance studies are required to detect rare events associated with vaccination.

PLAIN LANGUAGE SUMMARY

Vaccines for preventing rotavirus diarrhoea: vaccines in use

Rotavirus infection is a common cause of diarrhoea in infants and young children, and can cause mild illness, hospitalization, and death. Rotavirus infections results in approximately half a million deaths per year in children aged under five years, mainly in low- and

middle-income countries. Since 2009, the World Health Organization (WHO) has recommended that a rotavirus vaccine be included in all national immunization programmes.

This review evaluates a monovalent rotavirus vaccine (RV1; Rotarix, GlaxoSmithKline Biologicals) and a pentavalent rotavirus vaccine (RV5; RotaTeq, Merck & Co., Inc.). These vaccines have been evaluated in several large trials and are approved for use in many countries. No trials of the Lanzhou lamb rotavirus vaccine (LLR; Lanzhou Institute of Biomedical Products) were found; this vaccine is used in China only. The review includes 41 trials with 186,263 participants; all trials compared a rotavirus vaccine with placebo. The vaccines tested were RV1 (29 trials with 101,671 participants) and RV5 (12 trials with 84,592 participants). The trials took place in a number of worldwide locations.

In the first two years of life, RV1 prevented more than 80% of severe cases of rotavirus diarrhoea in low-mortality countries, and at least 40% of severe rotavirus diarrhoea in high-mortality countries. Severe cases of diarrhoea from all causes (such as any viral infection, bacterial infections, toxins, or allergies) were reduced after vaccination with RV1 by 35 to 40% in low-mortality countries, and 15 to 30% in high-mortality countries.

In the first two years of life, RV5 reduced severe cases of rotavirus diarrhoea by more than 80% in low-mortality countries, and by 40 to 57% in high-mortality countries. Severe cases of diarrhoea from all causes were reduced by 73% to 96% in low-mortality countries, and 15% in high-mortality countries, after vaccination with RV5. Diarrhoea is more common in high-mortality countries, so even modest relative effects prevent more episodes in this population. The vaccines when tested against placebo gave similar numbers of adverse events such as reactions to the vaccine, and other events that required discontinuation of the vaccination schedule.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Patient or population: children
Setting: low-mortality countries (WHO strata A & B)
Intervention: RV1
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	RV1				
Severe rotavirus diarrhoea Follow-up: up to 1 year	**12 per 1000**	**2 per 1000** (1 to 3)	**RR 0.14** (0.07 to 0.26)	40,631 (6 studies)	⊕⊕⊕⊕ **high**[1]	One study (RV1 Vesikari 2007a-EU) reported higher efficacy compared to the pooled data. When this study was excluded from the analysis, no heterogeneity was observed on the pooled data
Severe rotavirus diarrhoea Follow-up: up to 2 years	**22 per 1000**	**3 per 1000** (3 to 4)	**RR 0.15** (0.12 to 0.2)	32,854 (8 studies)	⊕⊕⊕⊕ **high**	
Severe episodes of all-cause diarrhoea Follow-up: up to 1 year	**34 per 1000**	**20 per 1000** (17 to 24)	**Rate Ratio 0.60** (0.5 to 0.72)	17,867 (1 study)	⊕⊕⊕○ **moderate**[2]	One additional European study reported on cases of children with severe all-cause diarrhoea (RR 0.48, 95% CI 0.37 to 0.61; 3874 participants, one study); this data could not be pooled with the study reporting on number of episodes

Severe episodes of all-cause diarrhoea Follow-up: up to 2 years	**39 per 1000**	**24 per 1000** (22 to 28)	**Rate Ratio 0.63** (0.56 to 0.71)	39,091 (2 studies)	⊕⊕⊕○ **moderate**[3]	Two additional studies reported on cases of children with severe all-cause diarrhoea (RR 0.49, 95% CI 0.40 to 0.60; 6269 participants, two studies) ; this data could not be pooled with the studies reporting on number of episodes
All-cause death Follow-up: 2 months to 2 years	**12 per 10,000**	**15 per 10,000** (10 to 21)	**RR 1.27** (0.89 to 1.81)	93,321 (18 studies)	⊕⊕○○ **low**[4]	
All serious adverse events Follow-up: 2 months to 2 years	**41 per 1000**	**37 per 1000** (34 to 39)	**RR 0.9** (0.84 to 0.95)	91,957 (20 studies)	⊕⊕⊕○ **moderate**[5]	
Serious adverse events: intussusception Follow-up: 2 months to 2 years	**66 per 100,000**	**57 per 100,000** (34 to 96)	**RR 0.87** (0.52 to 1.46)	91,832 (11 studies)	⊕⊕○○ **low**[6]	

*The basis for the **assumed risk** is the control group risk across studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High-quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate-quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low-quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low-quality: we are very uncertain about the estimate.

[1] Heterogeneity (I^2 = 66%) was observed in the pooled data, but given the strength of the evidence outcome was not downgraded.

[2] Downgraded by 1 for risk of selective reporting bias. Only two of the six studies reporting on severe rotavirus diarrhoea provided data for this outcome.

[3] Downgraded by 1 for risk of selective reporting bias. Only four of the eight studies reporting on severe rotavirus diarrhoea provided data for this outcome.

[4] Downgraded by 2 for imprecision. These trials were not powered to detect an effect on mortality.

[5] Downgraded by 1 for risk of bias. Fourteen of the 20 included studies did not sufficiently report method of allocation concealment, blinding or incomplete outcome data. One study was not double blinded and one study was at high risk of incomplete outcome data bias.

[6] Downgraded by 2 for imprecision. There was a 1:10,000 increased risk of intussusception with a previous rotavirus vaccine (<http://www.who.int/vaccines-documents/DocsPDF04/wwwSOWV_E.pdf>), therefore, these trials were not powered to detect an association between RV1 and intussusception.

BACKGROUND

The global impact of rotavirus infection

Rotavirus is the leading known cause of severe gastroenteritis in infants and young children worldwide (Vesikari 1997; Parashar 2006a; WHO 2007). It causes more than one-third of all diarrhoea-related hospital admissions (Parashar 2006a; Linhares 2008; Tate 2011) and an estimated 450,000 deaths per year, with most deaths occurring in developing countries (Parashar 2006a; Linhares 2008; Tate 2011). More deaths occur in resource-limited countries due to poor access to oral rehydration solution and medical facilities, and due to underlying conditions, such as malnutrition. However, in more industrialized countries, hospital admissions due to rotavirus gastroenteritis escalate with increasing income despite improved sanitation and hygiene (Malek 2006; Parashar 2006a).

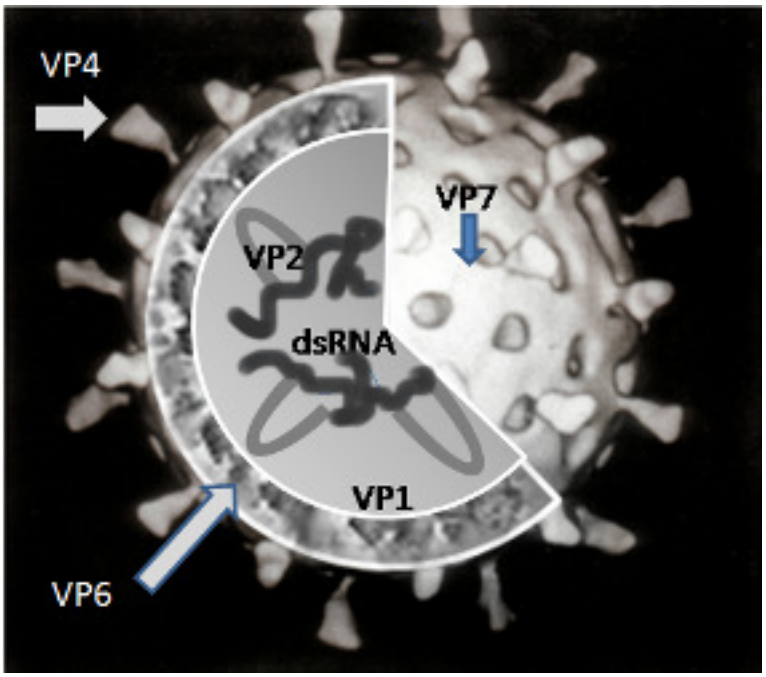
Epidemiological and clinical features of rotavirus infection

Rotavirus is transmitted primarily via the faecal-oral route with symptoms typically developing one to two days following infection. Most children become infected with rotavirus at least once within the first three years of life, and epidemiological studies depict a peak incidence of rotavirus diarrhoea between six and 24 months of age (CDC-ASIP 1999; Linhares 2008). In some countries, a significant number of hospitalizations associated with rotavirus disease occur in infants aged less than six months (Bresee 2005). Infection may be asymptomatic or result in a severe, life-threatening illness characterized by vomiting, fever, watery diarrhoea, and dehydration (AAP 1998). However, in the day-to-day clinical setting especially in developing countries, the distinction between all-cause diarrhoea and rotavirus diarrhoea may not be made, as tests for rotavirus infection may not be available or may not be routinely used.

Rotavirus strain diversity

Rotaviruses are double-stranded RNA viruses that evolve by point mutation, genetic reassortment, and interspecies transmission. While complete genomic analysis includes all eleven genome segments, the two proteins that together comprise the outer virus layer (VP7 and VP4) have been most extensively examined. The enormous diversity and capacity of human rotaviruses for change suggest that rotavirus vaccines must demonstrate protective efficacy against all of the major circulating strain types (de Quadros 2004) as well as new strains that will continue to emerge (Gentsch 2005). Out of at least 15 VP7 (G, for glycoprotein) types and 26 VP4 (P, for protease-sensitive) types that have been recognized in humans to date (see Figure 1 for details), five combinations of G and P type are prevalent worldwide: these are G1, G3, G4, G9 with P[8] VP4 type, and G2 P[4] strains (Santos 2005; Linhares 2008).

Figure 1. A simplified diagram of the location of rotavirus structural proteins (source: Graham Cohn, Wikipedia (public domain image)): Rotaviruses are segmented, double-stranded RNA viruses. The mature, triple-layered virus particle comprises a core (which contains the viral genome), a middle layer (comprised of viral protein (VP)6, and an outer layer (comprised of VP7 and VP4) as shown in the figure. VP6 defines rotavirus group, and most rotaviruses that infect humans are of group A. The two outer capsid proteins independently induce neutralizing antibodies: VP7, a glycoprotein, defines G-serotype; and the protease-sensitive VP4 protein defines P-serotype. G-serotype determined by serological methods correlates precisely with G-genotype obtained through molecular assays, whereas there is an imperfect correlation of P-serotype and P-genotype; P-genotype is thus included in square brackets.



A brief summary of the development of rotavirus vaccines

The first reports of clinical trials of rotavirus vaccine candidates, which were based on animal rotavirus, were published in the early 1980s.

Early vaccine candidates were single-strain animal viruses that replicate poorly in the human host. However, the efficacy of such 'monovalent' vaccines was highly variable, possibly due to a predominant homotypic (type-specific) response. In an effort to broaden the protection afforded by rotavirus vaccines, multivalent human-animal reassortant vaccines (created in cell culture through the insertion by reassortment of human rotavirus VP7 or VP4 genes into the backbone of bovine or rhesus monkey rotavirus strains), and attenuated strains of human rotaviruses were included in second-generation vaccines (Henchal 1996).

The rhesus-human tetravalent reassortant rotavirus vaccine (RRV-TV, RotaShield, Wyeth-Lederle, USA) was the first vaccine to be licensed (in 1998), but, due to an association with intussusception (described below), the vaccine was withdrawn from use in 1999. This withdrawal caused the rotavirus vaccine experts and other interested parties to meet and re-evaluate the direction of research (WHO/UNICEF 2003). The group recommended developing new rotavirus vaccine candidates with testing in developed and developing countries undertaken in parallel due to the differences in the epidemiology of rotavirus and the urgent need to introduce rotavirus vaccines in the world's poorest countries. They also recommended that the World Health Organization (WHO) encourage research activities on the pathogenesis and epidemiology of intussusception.

Vaccines approved for use

This review evaluates three vaccines: a monovalent rotavirus vaccine (RV1; Rotarix, GlaxoSmithKline Biologicals) and a pentavalent rotavirus vaccine (RV5; RotaTeq, Merck & Co., Inc.), which have been evaluated in several large trials and are approved for

use in many countries; and Lanzhou lamb rotavirus vaccine (LLR; Lanzhou Institute of Biomedical Products), which is approved for use in China only.

RV1 is an oral, live-attenuated, human rotavirus vaccine derived from the most common circulating wild-type strain G1P[8]. RV1 is based on a rotavirus of entirely human origin, and is administered to infants in two oral doses with an interval of at least four weeks between doses. The manufacturer states that the "vaccination course should preferably be given before 16 weeks of age, but must be completed by the age of 24 weeks" (EMA 2011). RV1 was approved first in Mexico (2004) and has since been approved in over 116 countries (GSK 2010 (press release)), including the USA (GSK 2008 (press release)) and European Union (GSK 2006 (press release)); and has been included in national immunization programmes in over 20 countries including Brazil, El Salvador, Mexico, Panama, South Africa, and Venezuela (GSK 2007 (press release); WHO 2011). In 2008, it was included in the WHO's list of vaccines for purchase by United Nations (UN) agencies (WHO 2008a).

RV5 is an oral, live, human-bovine, reassortant, multivalent, rotavirus vaccine developed from an original Wistar calf 3 (WC3) strain of bovine rotavirus. The vaccine contains five live, human-bovine reassortant rotavirus strains. Four reassortant rotavirus strains each express one of the common human VP7 (G) types including G1, G2, G3, and G4, and the fifth reassortant expresses the common human VP4 (P) type P[8]. The three-dose liquid vaccine is intended for infants aged between six and 32 weeks with the first dose given at six to 12 weeks and subsequent doses administered at four to 10 week intervals; however, the third dose should not be given after 32 weeks of age (Merck 2008 (press release)). RV5 has been approved in 97 countries around the world (Merck 2011), including the European Union (EMEA 2008) and USA (FDA 2008). It has been included in national immunization programmes in over 10 countries including the USA, Nicaragua, Belgium and most recently Iraq (WHO 2011). As with RV1, it was included in the WHO's November 2008 list of vaccines for purchase by UN agencies (WHO 2008a).

LLR is a live-attenuated, monovalent (G10 P[12]) vaccine derived from a lamb (WHO 2008b). This oral, three-dose vaccine was developed by the Lanzhou Institute of Biomedical Products in China and was licensed in China in 2000 (Fu 2007). There is a paucity of publicly available data regarding this vaccine.

Vaccines no longer in use

Several vaccines, including the first licensed rotavirus vaccine (RRV-TV; RotaShield, Wyeth Laboratories) were developed, tested in trials, and later abandoned or withdrawn from use; these are covered in a separate Cochrane Review (Soares-Weiser 2004). The first licensed rotavirus vaccine, RRV-TV, a tetravalent rhesus-human reassortant vaccine, was withdrawn from use in 1999 following reports of intussusception (bowel obstruction which occurs when one segment of bowel becomes enfolded within another segment). Evaluations have since suggested a strong age-related risk of intussusception, with 80% of intussusception cases occurring in infants who were more than 90 days old when the first vaccine dose was administered (Simonsen 2005). Although it is still currently licensed, this vaccine is no longer in clinical use (Dennehy 2008).

Rationale for rotavirus vaccination and recommendations

Vaccination is considered to be the intervention with the most potential for reducing the impact of rotavirus disease for several reasons. Although rotavirus infects most infants, predicting the progression of the disease to severe diarrhoea and dehydration is not possible. Moreover, improvements in hand hygiene and sanitation have limited impact on prevention of the disease (Vesikari 2008a). Also, other measures for the prevention of rotavirus gastroenteritis, such as passive immunization or probiotics, are only partially effective and are not suitable for large-scale use (Mrukowicz 2008). Vaccination of infants, before the first rotavirus infection, is therefore required to prevent most severe cases of the disease (Vesikari 2008a), with early and sustained protection required during the first two years of life (Linhares 2008).

Ideally, rotavirus vaccines would be given concomitantly with other childhood vaccines (eg polio virus vaccine) without affecting or being affected by them. Also, universal rotavirus vaccination would include special paediatric populations, such as preterm infants, malnourished children, and immunocompromised children (including those infected with human immunodeficiency virus (HIV)), and the vaccines should be safe and effective for these children.

Recommendations and guidelines for rotavirus vaccine use

Vaccination with RV1 and RV5 were first recommended in 2006 in Europe and the Americas, where the vaccines efficacy have been demonstrated. In April 2009, the WHO Strategic Advisory Group of Experts (SAGE) on Immunization recommended "the inclusion of rotavirus vaccination of infants into all national immunization programmes", with a stronger recommendation for countries where "diarrhoeal deaths account for $\geq$10% of mortality among children aged <5 years" (SAGE 2009). The WHO recommendation was the culmination of many years of research and development, and the prioritisation of the need for a rotavirus vaccine by the WHO, the Global Alliance for Vaccines and Immunization (GAVI), the US Centers for Disease Control and Prevention, and the Rotavirus Vaccine Program at the Program for Appropriate Technology in Health (PATH) (Vesikari 2008a). SAGE recommended administering the first dose of vaccine RV1 or RV5 to infants of six to 15 weeks of age, with the last dose administered

before 32 weeks of age (SAGE 2009). In April 2012, SAGE relaxed the age restricted recommendation and advised to vaccinate "as soon as possible after the age of six weeks" because "the current age restrictions for the first dose (< 15 weeks) and last dose (< 32 weeks) are preventing vaccination of many vulnerable children" (SAGE 2012).

Regional rotavirus vaccination guidelines include the European Society for Paediatric Infectious Diseases/European Society for Paediatric Gastroenterology, Hepatology, and Nutrition Evidence-Based Recommendations for Rotavirus Vaccination in Europe (Vesikari 2008a; Vesikari 2008b), and the American Academy of Pediatrics Guidelines for Use of Rotavirus Vaccine (AAP 2009).

Rotavirus biology

The enormous diversity and capacity of human rotaviruses for change suggest that rotavirus vaccines must demonstrate protective efficacy against all of the major circulating strain types (de Quadros 2004) as well as new strains that will continue to emerge (Gentsch 2005). Out of at least 15 VP7 (G) types and 26 VP4 (P) types that have been recognized to date (see Figure 1 for details), five combinations of G and P type are prevalent worldwide: these are G1, G3, G4, G9 with P[8] VP4 type, and G2 P[4] strains (Santos 2005; Linhares 2008). Early vaccine candidates were developed solely from single-strain animal viruses that replicate poorly in the human host, but the efficacy of such 'monovalent' vaccines was highly variable, possibly due to a predominant homotypic (type-specific) response. In an effort to broaden the protection afforded by rotavirus vaccines, multivalent human-animal reassortant vaccines (created in cell culture through the insertion of human rotavirus VP7 or VP4 genes into the backbone of bovine or rhesus monkey rotavirus strains through the process of reassortment), and attenuated strains of human rotaviruses were included in second-generation vaccines (Henchal 1996). Also, a higher titre and multiple doses of rotavirus vaccine have been suggested to be more efficacious (Vesikari 1997; Bresee 1999), and have been evaluated as part of the vaccine development.

Use with other childhood vaccines and special populations

Ideally, rotavirus vaccines would be given concomitantly with other childhood vaccines (eg polio virus vaccine) without affecting or being affected by them. Also, universal rotavirus vaccination would include special paediatric populations, such as preterm infants, malnourished children, and immunocompromised children (including those infected with human immunodeficiency virus (HIV)), and the vaccines should be safe and effective for these children.

Performance of oral rotavirus vaccines in developing countries

Many oral vaccines, including rotavirus vaccines, have demonstrated lower efficacy and immunogenicity in developing countries in Africa and Asia compared to more developed countries in North America, South America, and Europe (Levine 2010). A systematic review evaluating regional variation of rotavirus vaccine efficacy showed that there is a correlation between lower vaccine efficacy against severe rotavirus diarrhoea and high country child mortality rates (Fischer Walker 2011). Reduced vaccine efficacy in countries with higher child mortality rates could be due to a combination of factors, such as co-morbidities including malnutrition and HIV infection, higher prevalence of enteric pathogens that may interfere with vaccine "take", and maternally-derived rotavirus antibodies transmitted to the infant via breast milk or the placenta (Cunliffe 2007; Levine 2010).

Outcomes of interest

The safety and efficacy of the licensed vaccines for the prevention of rotavirus gastroenteritis in infants (healthy and special populations) have been assessed in several randomized controlled trials (RCTs) worldwide. The goal of the current review is to systematically assess these trials and evaluate vaccine efficacy against rotavirus diarrhoea, all-cause diarrhoea, and diarrhoea-related medical visits and hospitalization. We also examine the occurrence of deaths, serious adverse events, including intussusception, in order to provide decision-makers, clinicians, and care-givers with the relevant information to aid decisions about vaccine use.

Development of Cochrane systematic rotavirus vaccine reviews

The original systematic review of rotavirus vaccines (Soares-Weiser 2004) examined vaccines in use and other vaccines including those no longer in use or in development. The 2004 version of the review concluded that more trials were needed before routine vaccine use could be recommended. An update in 2009 included a new search, revised inclusion criteria (only vaccines in use in children), updated review methods and new authors; the review was updated again in 2010 with nine new studies (Soares-Weiser 2010). The 2010 version of the review concluded that RV1 and RV5 are both effective vaccines for the prevention of rotavirus diarrhoea. Another update in February 2012 added a further nine new studies, GRADE summary of findings tables and, again, new authors joined the team (Soares-Weiser 2012). The current update includes a new search, major restructuring of analyses, including re-evaluating primary outcomes in consultation with the WHO to reflect that vaccine efficacy profiles are different in countries with different mortality rates. In addition, the authors discovered that two of the included studies were included twice, but as different

publications; this was adjusted in this update (the study known in the previous version of the review as RV1 GSK[045] 2007-AS is the same as RV1 Zaman 2009-AS, and the study known in the previous version of the review as RV1 Vesikari 2010-EU is the same as RV1 Vesikari 2007a-EU).

OBJECTIVES

Primary objectives were to evaluate the efficacy of rotavirus vaccines approved for use (RV1, RV5, and LLR) for preventing rotavirus diarrhoea, all-cause diarrhoea and death in children up to one and up to two years old for low- and high-mortality countries, and to evaluate serious adverse events including intussusception for the same age and mortality groups. Secondary objectives were to evaluate the efficacy of rotavirus vaccines on hospital admission, and reactogenicity and immunogenicity profiles.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs.

Types of participants

Children (age as defined in the trials).

Types of interventions

Intervention

Vaccines approved in any country.

Control

Placebo, no vaccination, or other vaccine.

Types of outcome measures

Primary*

- Rotavirus diarrhoea: severe (as defined in trial report).
- All-cause diarrhoea: severe.
- All-cause death.
- Serious adverse events (that are fatal, life-threatening, or result in hospitalization); eg Kawasaki disease.
- Intussusception.

Secondary

- Rotavirus diarrhoea: of any severity.
- All-cause diarrhoea (as defined in trial report).
- Rotavirus diarrhoea: requiring hospitalization.
- All-cause diarrhoea: requiring hospitalization.
- Emergency department visit.
- Hospital admission: all-cause.
- Reactogenicity (capacity to produce an adverse reaction, such as fever, diarrhoea, and vomiting).
- Adverse events that require discontinuation of vaccination schedule.

Other

- Immunogenicity
  - Vaccine virus shedding in stool.
  - Seroconversion: conversion from seronegative to seropositive for anti-rotavirus IgA antibodies.
- Drop-outs.

* Primary outcome measures were selected in consultation with the WHO and were all stratified according to high- or low-mortality rate, based on WHO mortality strata (WHO 1999), and up to one and up to two years follow-up.

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and ongoing).

Dr Vittoria Lutje (Information Specialist, Cochrane Infectious Diseases Group) or KS-W searched the following databases using the search terms and strategy described in Appendix 1: Cochrane Infectious Diseases Group Specialized Register (10 May 2012); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2012, Issue 5); MEDLINE (via PubMed; 1966 to May 2012); EMBASE (1974 to 10 May 2012); LILACS (1982 to 10 May 2012); and BIOSIS (1926 to 10 May 2012). The International Clinical Trials Registry Platform (ICTRP) was also searched on 10 May 2012, and HB searched Clinicaltrials.gov Clinical Study Register (www.clinicaltrials.gov) on 28 May 2012 using 'rotavirus' as the search term.

We also checked the reference lists of all studies identified by the above methods.

Data collection and analysis

Selection of studies

Using an EndNote database containing the results of all search strategies, KS-W and HM independently screened the title, abstract, or keywords of each EndNote record identified with the search strategy, and retrieved the full text for potentially relevant trials and for records where the relevance was unclear. We created a form with the eligibility criteria in Microsoft Word 2003, which was piloted in five studies. KS-W and SN, IB-A, or EG independently applied the inclusion criteria to each potentially relevant trial to determine their eligibility, and we resolved any disagreements through discussion with HM. We tabulated the excluded studies along with the reason for excluding them in the section: Characteristics of excluded studies. We ensured that data from each trial were entered only once in our review.

Data extraction and management

We created a form for data collection in Microsoft Word 2003, which was piloted in five trials independently by two authors, and revised after the author team's discussion.

KS-W, HB, and SN extracted data and KS-W, IB-A, or EG cross-checked the data. All outcomes were dichotomous outcomes, and we extracted the total number of participants and number of participants that experienced the event. We compared the extracted data to identify errors. We resolved disagreements by consulting HM or KS-W. KS-W, EG, and HB entered data into Review Manager (RevMan).

Assessment of risk of bias in included studies

KS-W and HB, SN, IB-A, or EG independently assessed the risk of bias of each trial using The Cochrane Collaboration's risk of bias tool (Higgins 2008). Based on the guidance of the The Cochrane Collaboration's risk of bias tool (Higgins 2008), we created a form to make judgements on the risk of bias for the rotavirus diarrhoea outcome measure in six domains: sequence generation; allocation concealment; blinding (of participants, personnel, and outcome assessors); incomplete outcome data; selective outcome reporting; and other sources of bias. We categorized these judgements as 'yes' (low risk of bias), 'no' (high risk of bias), or 'unclear'. We resolved disagreements through discussion and by consulting HM or KS-W.

For the 2012 published version of this review, we asked for help from Dr Ana Maria Restrepo at the WHO Initiative for Vaccine Research, who contacted the vaccine manufacturers GlaxoSmithKline (RV1) and Merck (RV5), who were involved in designing and funding the majority of the included trials. We provided them with an Excel spreadsheet with specific details of each trial that would impact on the assessment of risk of bias. We received details from Merck (RV5), but so far have not received an answer from GlaxoSmithKline (RV1).

Measures of treatment effect

We analysed dichotomous data by calculating the risk ratio (RR) for each trial with the uncertainty in each result being expressed using 95% confidence intervals (CIs).

Unit of analysis issues

When trials had multiple treatment arms and it was considered suitable, we grouped the trial arms. We excluded irrelevant trial arms.

Dealing with missing data

We undertook a complete-case analysis (the number analysed) and an intention-to-treat analysis when data were available.

Assessment of heterogeneity

We initially assessed heterogeneity on the results of the trials by inspecting the graphical presentations and by calculating the Chi ^{2} test of heterogeneity. However, we were aware of the fact that the Chi^2 test has a poor ability to detect statistically significant heterogeneity among studies. Therefore, we also quantified the impact of heterogeneity in the meta-analysis using a measure of the degree of inconsistency in the studies' results (Higgins 2003). This measure (I^2 statistic) describes the percentage of total variation across studies that are due to heterogeneity rather than the play of chance (Higgins 2003). The I^2 values lie between 0% and 100%, and a simplified categorization of heterogeneity could be low, moderate, and high to I^2 values of 25%, 50%, and 75% respectively (Higgins 2003).

Assessment of reporting biases

If ten or more studies were included, we examined a funnel plot for the primary outcome (severe rotavirus diarrhoea) estimating the precision of trials (plotting the RR against the standard error (SE) of the log of RR) to estimate potential asymmetry.

Data synthesis

We stratified all analyses by the type of vaccine. Subsequently, we grouped all outcomes in the meta-analyses according to the time point when the outcome was measured and/or the number of rotavirus seasons as follows: less than two months; up to one year (one rotavirus season); one to two years (up to two rotavirus seasons); and more than three years (three rotavirus seasons). If

data were available for more than one time point, we used the number of completers for each time point in the trial.

For the current update, we stratified each primary outcome (rotavirus diarrhoea, all-cause diarrhoea, all-cause death, all serious adverse events, and intussusception) and selected secondary outcomes (rotavirus diarrhoea and all-cause diarrhoea of any severity, and all-cause hospitalization) by country mortality rate according to WHO mortality strata (WHO 1999) as follows:

1. Low-mortality: countries in WHO strata A and B (very low/low child mortality and low adult mortality);
2. High-mortality: countries in WHO strata D and E (high child mortality and high/very high adult mortality).

We did not identify any studies that were performed in countries with WHO stratum C (low child mortality and high adult mortality).

We used a fixed-effect model, unless we demonstrated statistically significant heterogeneity ($P < 0.10$) for a specific outcome, in which case we used the random-effects models.

We included separate analyses for cases of diarrhoea (eg a child who has diarrhoea regardless of the number of episodes) and episodes (ie one child can experience more than one episode) where data permitted. We combined episodes using the rate ratio and SE, with the uncertainty in each result being expressed using 95% CI.

Summary of findings tables

We interpreted the findings of this review using the GRADE approach (Schünemann 2008) and we used GRADE profiler (GRADE 2004) to import data from Review Manager (RevMan) to create 'Summary of findings' tables. These tables provide outcome-specific information concerning the overall quality of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on all outcomes we rated as important to patient-care and decision-making, and is reflected as follows: high-quality ("vaccine prevents...."); moderate-quality ("vaccine probably prevents..."); and low-quality ("vaccine may prevent....").

We selected primary outcomes, all stratified by vaccine and high or low country mortality, for inclusion in the 'Summary of findings' tables: severe rotavirus diarrhoea; severe all-cause diarrhoea ; all-cause death; serious adverse events; and intussusception.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses to assess the impact of the following possible sources of heterogeneity for any of the included vaccines: vaccine protection against specific rotavirus G types; and vaccination of special groups (preterm, immunocompromised (including HIV), breastfed, and children with malnutrition). For all but the last two subgroups, we created categorical variables and performed the subgroup analyses in Comprehensive Meta-Analysis (Version 2.2) using the analysis of variance model (Borenstein 2009). In a previous version of this review (Soares-Weiser 2010), we also analysed vaccine effect according to each study's country income status, use of other childhood vaccines, number of doses administered, and source of funding. These subgroup analyses did not show any differences, and are not presented in the current version; they can be found in Soares-Weiser 2010.

Sensitivity analysis

We also planned to conduct sensitivity analyses for the primary outcomes according to allocation concealment (high risk of bias, low risk of bias, and unclear) for outcomes on which data could not be pooled because of significant heterogeneity ($I^2 > 75\%$).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

We identified and included 41 independent trials (see Characteristics of included studies), located 25 ongoing studies (see Characteristics of ongoing studies), and excluded 60 articles for the reasons given in the Characteristics of excluded studies section.

The 41 trials enrolled about 186,263 participants (approximate number as some trials provided only the number evaluable), and each trial compared a rotavirus vaccine with a placebo. The vaccines tested were RV1 (29 trials reported in 130 publications or reports; 101,671 participants) and RV5 (12 trials reported in 47 publications or reports; 84,592 participants). None of the identified trials used LLR.

The trials were conducted around the world, and the location can be identified in the study reference: AF, Africa; AS, Asia; EU, Europe; INT, several international locations; LA, Latin America; NA, North America; or country three-letter acronym according to ISO 3166-1 Alpha-3 (eg BGD for Bangladesh) from http://www.all-acronyms.com/special/countries˙acronyms˙and˙abbreviations, if the study was conducted in a single country.

1. RV1

The 29 RV1 trials were published between 1998 and 2012. Five of the trials are unpublished and were located on the GlaxoSmithKline website via clinicalstudyresults.org. Twenty trials enrolled around 500 participants or less, two trials enrolled around 1000 participants, six trials enrolled between 2155 and 10,708 participants, and one large trial enrolled 63,225 participants. Most

children were aged between one and three months at the time of the first vaccination.

Outcome measures

Each trial reported on one or more of the outcome measures specified for this review (see Appendix 2). We included data on participants requiring medical visits as this was reported in some trials and is a similar outcome measure to participants requiring hospitalization.

Nineteen trials were safety studies, reporting mainly safety outcomes (eg serious adverse events and reactogenicity), immunogenicity outcomes, or both. Eleven of these trials also reported efficacy outcomes with a follow-up of up to two months. The other ten trials reported one or more efficacy outcomes (eg rotavirus diarrhoea) in addition to safety outcomes; most reported one or more immunogenicity outcomes. The trials varied in the length of follow-up, but in general the trials that specified efficacy outcome measures had longer follow-up times (Appendix 2).

As shown in Appendix 3, rotavirus diarrhoea (of any severity) was the most common efficacy outcome reported (by 18 trials); 11 trials reported on severe rotavirus diarrhoea, and nine reported on rotavirus diarrhoea requiring hospitalization. Data on all-cause diarrhoea were provided by ten trials, severe all-cause diarrhoea by five trials. Most reported all-cause death and drop-outs, but other efficacy outcomes were reported by few trials.

For safety outcomes (Appendix 4), all but three trials reported on reactogenicity, all but two trials reported on serious adverse events, and all but eight reported on adverse events leading to discontinuation of the intervention.

Most trials reported on one or more immunogenicity outcomes; see Appendix 4.

Location

Early trials were conducted in North America and Europe, but since 2005 trials have also been conducted in Asia (Bangladesh, India, Japan, Philippines, South Korea, Singapore, Thailand, Vietnam; 11 trials), Latin America (Argentina, Brazil, Chile, Colombia, Dominican Republic, Honduras, Mexico, Nicaragua, Panama, Peru, Venezuela; six trials), and Africa (South Africa, Malawi; four trials); see Appendix 5. Most trials had multiple sites, often in several countries; RV1 Vesikari 2007a-EU included 98 sites in six European countries.

Country mortality rate

Most trials were conducted in countries with low-mortality rates, corresponding to WHO mortality strata A and B. Six trials were conducted in countries with high-mortality rates, (RV1 Steele 2008-ZAF; RV1 Narang 2009-IND; RV1 Zaman 2009-BGD; RV1 Madhi 2010-AF; RV1 Steele 2010a-ZAF; RV1 Steele 2010b-ZAF) corresponding to WHO mortality strata D and E; see Appendix 5. For RV1 Madhi 2010-AF, when available, data were split between countries into RV1 Madhi 2010-MWI and RV1 Madhi 2010-ZAF. Two trials were conducted in several countries spanning both low- and high-mortality countries: RV1 GSK[033] 2007-LA was conducted in four study centres in a high-mortality country (Peru), but also in three study centres in two low-mortality countries (Colombia and Mexico) and was placed in the high-mortality group, and RV1 Ruiz-Palac 06-LA/EU was conducted mainly in low-mortality countries in Latin America and in Finland, but also in two high-mortality countries (Nicaragua and Peru) and was placed in the low-mortality group.

Vaccine schedule

The trials varied in the vaccine dose and schedule (see Appendix 6). Most trials gave two doses of the vaccine with virus concentration of more than 10^6 plaque-forming units (PFU). Older trials, conducted between 1998 and 2005, tended to include slightly lower PFU or a range of PFU for comparison.

RV1 was given as two doses in all but four trials: one trial conducted in partnership with GlaxoSmithKline and PATH Rotavirus Vaccine Program tested two and three doses of the vaccine (RV1 Madhi 2010-AF); another trial conducted by GlaxoSmithKline in which the poliovirus vaccine was co-administered with RV1, tested two or three vaccine doses to investigate differences in immune response (RV1 Steele 2010b-ZAF); a third study tested three vaccine doses in HIV-positive infants (RV1 Steele 2010a-ZAF); and a fourth study tested three vaccine doses in healthy infants (RV1 GSK[021] 2007-PAN).

Some trials compared more than one arm: different PFU virus concentrations (RV1 Vesikari 2004a-FIN; RV1 Dennehy 2005-NA; RV1 Phua 2005-SGP; RV1 Salinas 2005-LA; RV1 Ward 2006-USA); different formulations (RV1 GSK[021] 2007-PAN; RV1 GSK[033] 2007-LA; RV1 GSK[101555] 2008-PHL; RV1 Kerdpanich 2010-THA; RV1 Vesikari 2011-FIN); co-administration of other vaccine (RV1 Steele 2008-ZAF; RV1 Zaman 2009-BGD); and different intervals between doses (RV1 Anh 2011-PHL; RV1 Anh 2011-VNM).

Infant vaccination status

All but four trial reports referred to vaccination with other infant vaccines (see Appendix 6). Most trials co-administered other routine infant vaccines, such as diphtheria-tetanus-acellular pertussis, *Haemophilus influenzae* type b (HiB), inactivated polio vaccine, and hepatitis B vaccine (HBV). Some trials also co-administered oral polio vaccine. Other trials imposed a two-week separation between other infant vaccines and rotavirus vaccine or placebo, or specified other vaccines as not allowed.

Methods for collecting adverse event data

Twelve of the 29 trials did not provide details of how adverse event data were collected. Out of the trials that did report the method of collecting adverse event data, nine trials used passive methods (eg diary cards), two used an active method ("active surveillance system"), and five used both passive and active methods (eg diary card plus regular telephone calls to parents); see Appendix 7.

Source of funding

Most trials were supported by GlaxoSmithKline Biologicals, two of which were in partnership with PATH Rotavirus Vaccine Program (RV1 Zaman 2009-BGD; RV1 Madhi 2010-AF), and another two in partnership with RAPID trials and WHO (RV1 Steele 2008-ZAF; RV1 Steele 2010a-ZAF). Three trials were sponsored by Avant Immunotherapeutics (formerly Virus Research Institute, Inc.) (RV1 Bernstein 1998-USA; RV1 Bernstein 1999-USA; RV1 Ward 2006-USA).

2. RV5

We identified 12 trials of RV5 vaccine. The earliest was reported in 2003 and the most recent in 2010. Three of the trials are unpublished and were accessed via clinicalstudyresults.org or clinicaltrials.gov. Overall, 84,592 participants were included in the trials; the largest trial included 70,301 participants (RV5 Vesikari 2006b-INT) and the smallest included 48 participants (RV5 NCT00953056 2010-CHI). All but one trial enrolled children aged between one and three months; the children in RV5 Vesikari 2006a-FIN were aged between three and six months. For the 2012 published version of this review, we received new information from Merck (Merck 2012) for some of the trials on the outcomes serious adverse events, intussusception, and deaths. The new information has been incorporated into the analyses and indicated in the Characteristics of included studies section.

Outcome measures

Four trials were safety studies (Appendix 2) reporting safety outcomes (eg serious adverse events and reactogenicity) and generally immunogenicity outcomes as well. The other eight trials reported one or more efficacy and safety outcomes, and seven out of those eight reported immunogenicity outcomes also (Appendix 2). The trials varied in the length of follow-up (Appendix 2), but in general the trials that specified efficacy outcome measures had longer follow-up times (up to three years). As for the RV1 trials, we included data on participants requiring medical visits as this was reported in some trials and is a similar outcome measure to participants requiring hospitalization.

As shown in Appendix 3, rotavirus diarrhoea - severe cases and cases of any severity - were the most common efficacy outcomes reported (by eight trials); only one of these reported rotavirus diarrhoea requiring hospitalization. Three trials provided data on severe cases of all-cause diarrhoea; two also presented data on cases with any severity. Nine trials reported all-cause death, and 10 of the 12 trials reported drop-outs.

For safety outcomes, all trials reported on serious adverse events and reactogenicity, but four did not provide data on adverse events leading to discontinuation of the intervention; see Appendix 4.

Ten trials reported on an immunogenicity outcome (Appendix 4).

Location

Half of the trials were conducted in low-mortality countries in North America and Europe. Six trials, including the smallest and the largest trials, were conducted in other regions: RV5 Armah 2010-AF was conducted in Ghana, Kenya and Mali; RV5 Kim 2008-KOR was conducted in South Korea; RV5 NCT00718237 2010-JPN was conducted in Japan; RV5 NCT00953056 2010-CHI was conducted in China; RV5 Vesikari 2006b-INT was conducted in 12 countries in Asia, the Caribbean, Europe, Latin America, North America; and RV5 Zaman 2010-AS was conducted in Bangladesh and Vietnam. Each trial had multiple sites, ranging from three (RV5 Vesikari 2006a-FIN) to 356 sites (RV5 Vesikari 2006b-INT); see Appendix 5.

Country mortality rate

Most trials were conducted in countries with low-mortality rates, corresponding to WHO mortality strata A and B; see Appendix 5. Three trials were conducted in several countries spanning both low- and high-mortality countries. RV5 Armah 2010-AF was conducted in three high-mortality countries, Ghana, Kenya, and Mali, and when available data were split into RV5 Armah 2010-GHA, RV5 Armah 2010-KEN and RV5 Armah 2010-MLI. RV5 Vesikari 2006b-INT was conducted mainly in European and Latin American low-mortality countries, but also in Guatemala, a high-mortality country, and was placed in the low-mortality group. RV5 Zaman 2010-AS was conducted in one high-mortality country (Bangladesh) with 1136 participants, and in one low-mortality country (Vietnam) with 900 participants, and was placed in the high-mortality group, except when data could be split into RV5 Zaman 2010-BGD and RV5 Zaman 2010-VNM.

Vaccine schedule

Each trial used three doses of RV5 vaccine, with intervals between doses of four and 10 weeks (see Appendix 6). All but one trial had one vaccine and one placebo arm; RV5 Vesikari 2006a-FIN included three vaccine arms in which there were different RV5 components (G1-4, P1A, G1-4, and P1A).

Infant vaccination status

Most trials did not restrict the use of other childhood vaccines, see Appendix 6. One trial co-administered hepatitis B, diphtheria-tetanus-acellular pertussis, poliovirus, and *H. influenzae* type

b vaccines with RV5 (RV5 Ciarlet 2009-EU). Two trials allowed the use of other licensed childhood vaccines, including oral polio vaccine (RV5 Armah 2010-AF; RV5 Zaman 2010-AS). Three trials did not allow the use of other vaccines (RV5 Clark 2003-USA; RV5 Clark 2004-USA; RV5 NCT00953056 2010-CHI), and one trial did not mention their use (RV5 NCT00718237 2010-JPN).

Methods for collecting adverse event data

As shown in Appendix 7, six trials used a combination of passive methods (eg diary cards for parents) and active methods (directly contacting parents) to collect adverse event data. The other trials used passive methods only (diary cards, two trials), active methods only ("active surveillance", two trials), or the information was not provided (two trials).

Source of funding

All trials were funded by Merck & Co., Inc. Two of those trials also received funding and were run by PATH (GAVI Alliance grant) (RV5 Armah 2010-AF; RV5 Zaman 2010-AS).

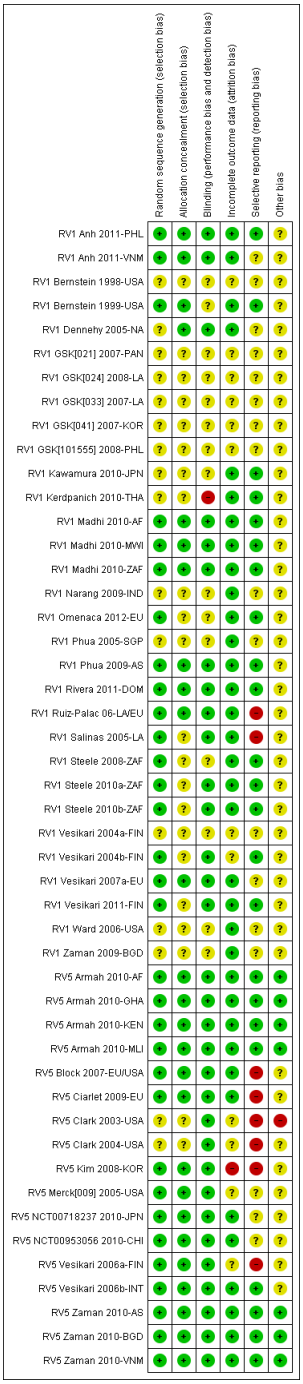
Ongoing studies

We identified 25 ongoing trials, 14 of RV1, one of RV5 and ten others (RV1 together with RV5; RV3-BB; ORV 116E; Brazilian Rotavirus vaccine; RotaVac and BRV-TV) (see Characteristics of ongoing studies). As shown in Appendix 8, the RV1 trials are being conducted in Africa (four), Asia (six), and Europe (three). The ongoing RV5 trial is in Africa, and the studies testing other vaccines are located in Australia, Brazil, India, New Zealand, South Africa, and the USA.

Risk of bias in included studies

We prepared a risk of bias assessment for each trial, with a focus on the rotavirus diarrhoea outcome measure. Of the 41 RCTs analysed in this review, 25 (61%) reported an adequate generation of allocation sequence, while the method of assignment was unclear in the remaining studies. The methods used to conceal allocation were considered adequate in 19 trials (46%), and unclear in the remaining studies. Information about blinding of participants, care providers, or outcome assessors was provided and we considered it to be adequate in 25 studies (61%), unclear for 15 studies, and not double-blind for one study (RV1 Kerdpanich 2010-THA). Incomplete outcome data was adequately addressed in 28 studies (68%), unclear in 12 studies, and was not addressed adequately in one study. Sixteen trials were free from selective reporting bias, eight were not, and the remaining trials were unclear. Most trials were sponsored by the industry and it was not possible to assess if they were free of other biases; two recent trials performed in Africa were considered free from other biases (RV5 Armah 2010-AF; RV5 Zaman 2010-AS). An overall pictorial summary of the risk of bias assessment is shown in Figure 2.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



RV1

For all the GlaxoSmithKline unpublished studies (five of the 29 trials) and seven published trials (RV1 Bernstein 1998-USA; RV1 Vesikari 2004a-FIN; RV1 Phua 2005-SGP; RV1 Ward 2006-USA; RV1 Narang 2009-IND; RV1 Zaman 2009-BGD; RV1 Kawamura 2010-JPN), little or no information was available about each criterion, which meant that we had to assess them as unclear. Generally, the published trials provided more information for assessment. We assessed nine of the remaining 17 trials as having a low risk of bias for three or more criteria, including allocation concealment (RV1 Bernstein 1999-USA; RV1 Dennehy 2005-NA; RV1 Ruiz-Palac 06-LA/EU; RV1 Vesikari 2007a-EU; RV1 Phua 2009-AS; RV1 Madhi 2010-AF; RV1 Anh 2011-PHL; RV1 Anh 2011-VNM; RV1 Rivera 2011-DOM). Three trials were assessed as high risk of bias; one trial for blinding (RV1 Kerdpanich 2010-THA), and two trials for selective reporting bias (RV1 Ruiz-Palac 06-LA/EU; RV1 Salinas 2005-LA).

RV5

Based on unpublished information provided by Merck, many of the trials' risk of bias could be upgraded for the current update of this review. Details of the new information is indicated in the risk of bias tables in the Characteristics of included studies section. Ten of the twelve RV5 trials were assessed as having a low risk of bias for sequence generation, allocation concealment and blinding, and varying risk of bias for attrition, selective reporting and other bias.Two of these trials (RV5 Armah 2010-AF; RV5 Zaman 2010-AS) were assessed as having an overall low risk of bias. The remaining two trials (RV5 Clark 2003-USA; RV5 Clark 2004-USA) both had low risk of bias for blinding of participants and personnel, but a mixed risk of bias for the remaining categories ranging from high to low. Six of all 12 RV5 trials had a high risk of bias for one or more criteria, most commonly a high risk of selective reporting.

Effects of interventions

See: **Summary of findings for the main comparison** RV1 compared to placebo for preventing rotavirus diarrhoea in low-mortality countries; **Summary of findings 2** RV1 compared to placebo for preventing rotavirus diarrhoea in high-mortality countries; **Summary of findings 3** RV5 compared to placebo for preventing rotavirus diarrhoea in low-mortality countries; **Summary of findings 4** RV5 compared to placebo for preventing rotavirus diarrhoea in high-mortality countries

1. RV1

1.1. Primary outcomes

1.1.1. Rotavirus diarrhoea: severe

Eleven trials provided data regarding the efficacy of RV1 to prevent severe rotavirus diarrhoea in children; see Analysis 1.1 for up to 1 year follow-up and Analysis 1.2 for two years follow-up. Trials were performed in low-mortality countries (RV1 Bernstein 1999-USA; RV1 Vesikari 2004b-FIN; RV1 Phua 2005-SGP; RV1 Salinas 2005-LA; RV1 Ruiz-Palac 06-LA/EU; RV1 Vesikari 2007a-EU; RV1 GSK[024] 2008-LA; RV1 Phua 2009-AS; RV1 Kawamura 2010-JPN;), and high-mortality countries (RV1 Madhi 2010-MWI; RV1 Madhi 2010-ZAF; RV1 Steele 2010b-ZAF). Data below are grouped accordingly.

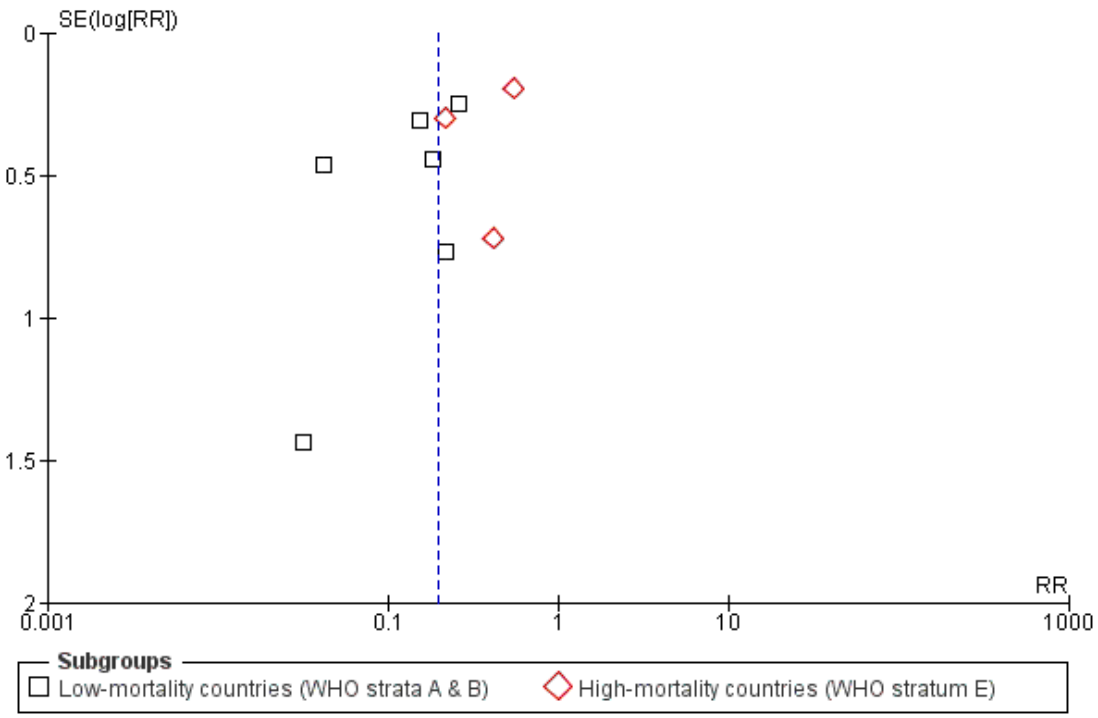
Low-mortality countries (WHO strata A & B)

RV1 reduced severe rotavirus diarrhoea by 86% after both one (RR 0.14, 95% CI 0.07 to 0.26; 40,631 participants, six trials) and two years (RR 0.15, 95% CI 0.12 to 0.20; 32,854 participants, eight trials). After three years there was no statistically significant difference between RV1 and placebo (RR 0.10, 95% CI 0.01 to 1.52; 12,109 participants, two trials (RV1 Phua 2009-AS and RV1 Vesikari 2007a-EU; data not shown)). Pooled results were significantly heterogeneous at one year (I^2 = 66%, Analysis 1.1) and three years (I^2 = 69%, data not shown) follow-up.

High-mortality countries (WHO stratum E)

RV1 reduced rotavirus diarrhoea by 63% during the first year of follow-up (RR 0.37, 95% CI 0.18 to 0.75; 5414 participants, two trials) and by 42% after two years (RR 0.58, 95% CI 0.42 to 0.79; 2764 participants, one trial). Pooled results were significantly heterogeneous at one year follow-up (I^2 = 70%, Analysis 1.1).
A funnel plot assymmetry was observed for trials reporting results up to one year (Figure 3).

Figure 3. Funnel plot of comparison: 1 RV1 versus placebo, outcome: 1.1 Rotavirus diarrhoea: severe (up to 1 year follow-up).



1.1.2. All-cause diarrhoea: severe

Severe all-cause diarrhoea was reported as cases in three trials (RV1 Phua 2005-SGP; RV1 Vesikari 2007a-EU; RV1 Madhi 2010-AF) and as episodes in two trials (RV1 Ruiz-Palac 06-LA/EU; RV1 Phua 2009-AS). We have reported these data separately. Trials were performed in low-mortality countries (RV1 Phua 2005-SGP; RV1 Ruiz-Palac 06-LA/EU; RV1 Vesikari 2007a-EU; RV1 Phua 2009-AS), and in high-mortality countries (RV1 Madhi 2010-MWI; RV1 Madhi 2010-ZAF).

Low-mortality countries (WHO strata A & B)

RV1 reduced the number of severe cases of all-cause diarrhoea by 52% at one year (RR 0.48, 95% CI 0.37 to 0.61; 3874 participants, one trial; Analysis 1.3), by 51% at two years (RR 0.49, 95% CI 0.40 to 0.60; 6269 participants, two trials; Analysis 1.4). RV1 reduced the number of severe episodes of all-cause diarrhoea by 40% at one year (rate ratio 0.60, 95% CI 0.50 to 0.72; 17,867 participants, one trial; Analysis 1.5), and by 37% at two years (rate ratio 0.63, 95% CI 0.56 to 0.71; 39,091 participants, two trials; Analysis 1.6). One trial reported on severe all-cause diarrhoea after three years follow-up (RV1 Phua 2009-AS), RV1 reduced severe cases by 27% (RR 0.73, 95% CI 0.61 to 0.88; 10,519 participants; data not shown).

High-mortality countries (WHO stratum E)

RV1 reduced the number of severe cases of all-cause diarrhoea by 30% at one year follow-up (RR 0.66, 95% CI 0.44 to 0.98; 4939 participants, one trial; Analysis 1.3), and by 17% at two years follow-up (RR 0.82, 95% CI 0.71 to 0.95; 2764 participants, one trial; Analysis 1.4). Pooled results were significantly heterogeneous at one year follow-up (I^2 = 82%).

1.1.3. All-cause death

Twenty-five trials reported on all-cause death, either as the number of deaths (RV1 Bernstein 1999-USA; RV1 Phua 2005-SGP; RV1 Vesikari 2007a-EU; RV1 Phua 2009-AS; RV1 Madhi 2010-AF; RV1 Steele 2010a-ZAF) or, in most trials, as fatal serious adverse events (RV1 Vesikari 2004b-FIN; RV1 Salinas 2005-LA; RV1 Ruiz-Palac 06-LA/EU; RV1 GSK[041] 2007-KOR; RV1 GSK[033] 2007-LA; RV1 GSK[021] 2007-PAN; RV1 GSK[024]

2008-LA; RV1 GSK[101555] 2008-PHL; RV1 Steele 2008-ZAF; RV1 Narang 2009-IND; RV1 Zaman 2009-BGD; RV1 Kawamura 2010-JPN; RV1 Kerdpanich 2010-THA; RV1 Steele 2010b-ZAF; RV1 Anh 2011-PHL; RV1 Anh 2011-VNM; RV1 Rivera 2011-DOM; RV1 Vesikari 2011-FIN; RV1 Omenaca 2012-EU). Number of deaths and fatal serious adverse events were pooled; see Analysis 1.7. Details of causes of death for each trial are presented in Appendix 9. Most trials were performed in low-mortality countries, and seven trials in high-mortality countries (RV1 GSK[033] 2007-LA; RV1 Steele 2008-ZAF; RV1 Narang 2009-IND; RV1 Zaman 2009-BGD; RV1 Madhi 2010-AF; RV1 Steele 2010a-ZAF; RV1 Steele 2010b-ZAF).

Low-mortality countries (WHO strata A & B)

There was no statistically significant difference in all-cause death between the two arms (18 trials, 93,321 participants).

High-mortality countries (WHO strata D & E)

There was no statistically significant difference in all-cause death between the two arms (7 trials, 7481 participants).

1.1.4. All serious adverse events

The total number of serious adverse events were reported in 27 trials, performed in low-mortality countries (RV1 Bernstein 1998-USA; RV1 Vesikari 2004a-FIN; RV1 Vesikari 2004b-FIN; RV1 Dennehy 2005-NA; RV1 Phua 2005-SGP; RV1 Salinas 2005-LA; RV1 Ruiz-Palac 06-LA/EU; RV1 GSK[041] 2007-KOR; RV1 GSK[021] 2007-PAN; RV1 Vesikari 2007a-EU; RV1 GSK[024] 2008-LA; RV1 GSK[101555] 2008-PHL; RV1 Phua 2009-AS; RV1 Kawamura 2010-JPN; RV1 Kerdpanich 2010-THA; RV1 Rivera 2011-DOM; RV1 Anh 2011-PHL; RV1 Anh 2011-VNM; RV1 Vesikari 2011-FIN; RV1 Omenaca 2012-EU), and in high-mortality countries (RV1 GSK[033] 2007-LA; RV1 Steele 2008-ZAF; RV1 Narang 2009-IND; RV1 Zaman 2009-BGD; RV1 Madhi 2010-AF; RV1 Steele 2010a-ZAF; RV1 Steele 2010b-ZAF); see Analysis 1.8.

Low-mortality countries (WHO strata A & B)

Fewer children allocated to RV1 had serious adverse events compared with placebo (RR 0.90, 95% CI 0.84 to 0.95; 91,957 participants, 20 trials).

High-mortality countries (WHO strata D & E)

There was no statistically significant difference in the number of serious adverse events between the two arms (RR 0.89, 95% CI 0.76 to 1.04; 7481 participants, seven trials).

1.1.5. Serious adverse events: intussusception

Twelve trials reported cases of intussusception. Trials were performed in low-mortality countries (RV1 Vesikari 2004b-FIN; RV1 Dennehy 2005-NA; RV1 Phua 2005-SGP; RV1 Salinas 2005-LA; RV1 Ruiz-Palac 06-LA/EU; RV1 Vesikari 2007a-EU; RV1 GSK[024] 2008-LA; RV1 Phua 2009-AS; RV1 Kawamura 2010-JPN; RV1 Rivera 2011-DOM), and in high-mortality countries (RV1 Madhi 2010-AF; RV1 Steele 2010b-ZAF); see Analysis 1.9.

Low-mortality countries (WHO strata A & B)

Twenty-nine cases of intussusception were reported in a total of 49,355 children in the RV1 arm compared with 28 cases of intussusception in 42,477 children of the placebo arm. Pooled results showed no increased risk for intussusception in children receiving RV1 when compared to placebo (RR 0.87, 95% CI 0.52 to 1.46; 91,832 participants, 11 trials).

High-mortality countries (WHO stratum E)

One case of intussusception was reported in a total of 3677 children in the RV1 arm compared with no cases of intussusception in 1737 children in the placebo arm. Pooled results showed no increased risk for intussusception in children receiving RV1 when compared to placebo (RR 1.49, 95% CI 0.06 to 36.63; 5414 participants, two trials).

1.2. Secondary outcomes

1.2.1 Serious adverse events: Kawasaki disease

Three trials reported four cases of Kawasaki disease among 7701 children allocated to RV1 compared to no cases in 5416 children allocated to placebo (RV1 Phua 2005-SGP; RV1 Salinas 2005-LA; RV1 Phua 2009-AS). We did not observe a statistically significant difference between the intervention and placebo group (RR 1.79, 95% CI 0.30 to 10.61; 13,117 participants, three trials; Analysis 1.10).

1.2.2. Serious adverse events requiring hospitalization

Two trials reported serious adverse events requiring hospitalization (RV1 Ruiz-Palac 06-LA/EU; RV1 Steele 2008-ZAF) and found fewer events in the RV1 group than the placebo group (RR 0.88,

95% CI 0.81 to 0.96; 63,675 participants, two trials; Analysis 1.11).

1.2.3 Rotavirus diarrhoea of any severity

Eighteen trials provided data regarding the efficacy of RV1 to prevent rotavirus diarrhoea in children; see Analysis 1.12 for two months safety trial follow-up, Analysis 1.13 for one year follow-up and Analysis 1.14 for two years follow-up. Trials were performed in low-mortality countries (RV1 Bernstein 1999-USA; RV1 Vesikari 2004b-FIN; RV1 Phua 2005-SGP; RV1 Salinas 2005-LA; RV1 GSK[041] 2007-KOR; RV1 Vesikari 2007a-EU; RV1 GSK[101555] 2008-PHL; RV1 Kerdpanich 2010-THA; RV1 Anh 2011-PHL; RV1 Anh 2011-VNM; RV1 Rivera 2011-DOM; RV1 Vesikari 2011-FIN; RV1 Omenaca 2012-EU), and in high-mortality countries (RV1 Narang 2009-IND; RV1 Zaman 2009-BGD; RV1 Madhi 2010-MWI; RV1 Madhi 2010-ZAF; RV1 Steele 2010a-ZAF; RV1 Steele 2010b-ZAF). Data below are grouped accordingly.

Low-mortality countries (WHO strata A & B)

Safety trials (up to two months follow-up): RV1 was not superior to placebo in the prevention of rotavirus diarrhoea in the trials assessing outcomes up to two months after vaccination (RR 1.28, 95% CI 0.66 to 2.50; 2853 participants, eight trials). These trials, although reporting cases of rotavirus diarrhoea, were not designed to measure efficacy.

Efficacy trials (one to three years follow-up): RV1 reduced rotavirus diarrhoea by 81% at up to one year (RR 0.19, 95% CI 0.08 to 0.47; 5935 participants, three trials) and 67% at the second year of follow-up (RR 0.33, 95% CI 0.21 to 0.50; 7293 participants, five trials). Pooled results, however, were significantly heterogeneous at one year (I^2 = 86%, Analysis 1.13) and two years (I^2 = 52%, Analysis 1.14) of follow-up. At the third year of follow-up, there were very few reported cases of rotavirus diarrhoea of any severity. Based on a single trial (RV1 Vesikari 2007a-EU, 1590 participants), there was no difference between RV1 and placebo groups (data not shown).

High-mortality countries (WHO strata D & E)

Safety trials (up to two months follow-up): Three trials found no difference in the RV1 group compared to placebo when outcomes were assessed up to two months after vaccination (RR 1.00, 95% CI 0.41 to 2.41; 757 participants, two trials).

Efficacy trials (one to two years follow-up): RV1 reduced rotavirus diarrhoea by 55% during the first year of follow-up (RR 0.45, 95% CI 0.28 to 0.73; 5414 participants, three trials), and by 59% during the second year (RR 0.41, 95% CI 0.28 to 0.62; 1251 participants, one trial). Pooled results were significantly heterogeneous at one year follow-up (I^2 = 81%, Analysis 1.13).

1.2.4. All-cause diarrhoea: of any severity

This outcome was reported as cases in eight trials from low-mortality countries (RV1 Vesikari 2004b-FIN; RV1 Phua 2005-SGP; RV1 Salinas 2005-LA; RV1 Kerdpanich 2010-THA; RV1 Anh 2011-PHL; RV1 Anh 2011-VNM; RV1 Vesikari 2011-FIN; RV1 Rivera 2011-DOM), in one trial from a high-mortality country (RV1 Steele 2010a-ZAF), and as episodes in three of the eight trials from low-mortality countries (RV1 Vesikari 2004b-FIN; RV1 Salinas 2005-LA; RV1 Rivera 2011-DOM). We have reported these data separately.

Low-mortality countries (WHO strata A & B)

Safety trials (up to two months follow-up): RV1 was not better than placebo in reducing the number of cases of all-cause diarrhoea at two months (2348 participants, five trials; Analysis 1.15).

Efficacy trials (one to two years follow-up): RV1 was not better than placebo in reducing the number of cases of all-cause diarrhoea at one year follow-up (2204 participants, two trials, Analysis 1.16), or after two years (2789 participants, two trials; Analysis 1.17).Two trials reported the number of episodes, with no statistically significant benefit with RV1 when compared to placebo at one year (2204 participants, two trials; Analysis 1.18) or at two years (736 participants, one trial; Analysis 1.19).

High-mortality countries (WHO stratum E)

Safety trials (up to two months follow-up): RV1 was not better than placebo in reducing the number of cases of all-cause diarrhoea at two months (100 participants, one trial; Analysis 1.15).

1.2.5. All-cause hospitalizations

One trial, performed in Singapore (RV1 Phua 2005-SGP) provided data regarding the efficacy of RV1 to prevent all-cause hospitalizations.

Low-mortality countries (WHO stratum A)

RV1 reduced hospitalizations in the second year of follow-up by 64% (RR 0.36, 95% CI 0.15 to 0.86; 2421 participants, one trial; Analysis 1.20).

1.2.6. Rotavirus diarrhoea: requiring hospitalization or medical attention

Hospitalizations were reduced by 81% after one year (RR 0.19, 95% CI 0.08 to 0.43; 39,260 participants, six trials), 86% at two years (RR 0.14, 95% CI 0.09 to 0.23; 32,183 participants, six trials), and 95% at three years (RR 0.05, 95% CI 0.02 to 0.16; 10,519 participants, one trial (RV1 Phua 2009-AS, data not shown)); pooled results were significantly heterogeneous at one year of follow-up (I^2 = 63%); see Analysis 1.21.

RV1 reduced medical visits by 92% at one year (RR 0.08, 95% CI 0.04 to 0.16; 3874 participants, one trial) and 78% at two years (RR 0.22, 95% CI 0.16 to 0.31; 7017 participants, three trials); see Analysis 1.22.

1.2.7. All-cause diarrhoea: requiring hospitalization

There was no significant difference between RV1 and placebo regarding cases of hospitalization for all-cause diarrhoea (14,393 participants, two trials; Analysis 1.23). At two years follow-up, RV1 reduced cases by 48% (RR 0.52, 95% CI 0.27 to 0.99; 14,367 participants, two trials; Analysis 1.23). RV1 Phua 2009-AS reported hospitalizations due to all-cause diarrhoea at three years follow-up, RV1 reduced hospitaizations by 28% (RR 0.72, 95% CI 0.59 to 0.86; 10,519 participants, data not shown). Pooled results were significantly heterogeneous at one year (I^2 = 83%) and at two years follow-up (I^2 = 77%).

RV1 Ruiz-Palac 06-LA/EU presented data on the number of episodes (Analysis 1.24); RV1 reduced hospitalizations by 42% at one year (rate ratio 0.58, 95% CI 0.47 to 0.71; 17,867 participants, one trial) and 47% at two years (rate ratio 0.53, 95% CI 0.46 to 0.61; 14,286 participants, one trial).

1.2.8. Reactogenicity

The occurrence of fever (Analysis 1.25), diarrhoea (Analysis 1.26), and vomiting (Analysis 1.27) were evaluated at several time points: after the first dose, after the second dose, after the third dose, and at the end of the follow-up period. Most trials contributed data to these outcomes. There were similar results for RV1 and placebo for each outcome and time point.

1.2.9. Adverse events that require discontinuation of vaccination schedule

There was no statistically significant difference between RV1 and placebo in the number of adverse events leading to discontinuation of the vaccination schedule (RR 1.07, 95% CI 0.86 to 1.34; 90,604 participants, 21 trials; Analysis 1.28).

1.3. Immunogenicity

Data on immunogenicity was not stratified by WHO strata. RV1 was more immunogenic than placebo when measured by vaccine virus shedding at the end of follow-up (RR 12.07, 95% CI 5.23 to 27.85; 2606 participants, 15 trials; Analysis 1.29), although the results were significantly heterogeneous (I^2 = 77%, Analysis 1.29). It was also more immunogenic when measured by seroconversion at all time points (Analysis 1.30); although the pooled data were significantly heterogeneous after dose one (I^2 = 57%) and two (I^2 = 82%).

1.4. Drop-outs before the end of trial

Twenty-two trials reported on the number of participants who dropped out of the trial before it ended. Overall, there was no statistically significant difference between the RV1 and placebo groups (RR 0.91, 95% CI 0.81 to 1.02; 25,005 participants, 22 trials; Analysis 1.31).

1.5. Subgroup analyses

1.5.1. G type

Rotavirus diarrhoea: of any severity

There were significantly fewer episodes of rotavirus diarrhoea of any severity in the group receiving RV1 when compared to placebo, regardless of G type; however, the pooled data for G1 and G9 types were significantly heterogeneous (I^2 = 66% and 81% respectively), see Analysis 1.32.

Rotavirus diarrhoea: severe

There were significantly fewer severe episodes of rotavirus diarrhoea in the RV1 groups compared with placebo in all episodes attributed to the G1 type (RR 0.20, 95% CI 0.11 to 0.37; 36,100 participants, five trials), G2 type (RR 0.40, 95% CI 0.16 to 0.98; 37,117 participants, four trials), and G9 type (RR 0.15, 95% CI 0.07 to 0.33; 19,250 participants, three trials); see Analysis 1.33. Results were not statistically significant for G3 types (12,940 participants, two trials) or for G4 types (2421 participants, one trial). The pooled data for G3 types were significantly heterogeneous (I^2 = 72%), with the larger of the two included trials (RV1 Phua 2009-AS) reporting a statistically significant difference favouring RV1, whereas the smaller trial (RV1 Phua 2005-SGP) reported no statistically significant difference.

1.5.2. Malnourished children

Rotavirus diarrhoea: of any severity

One trial, RV1 Salinas 2005-LA, provided data separately as the number of cases of rotavirus diarrhoea of any severity in a subgroup of malnourished children. RV1 was significantly better than placebo in preventing rotavirus diarrhoea for this subgroup at one year of follow-up (RR 0.39, 95% CI 0.19 to 0.79; 287 participants, Analysis 1.34).

1.5.3. Children infected with HIV

Rotavirus diarrhoea: of any severity

One safety trial, RV1 Steele 2010a-ZAF, included only confirmed HIV-positive, asymptomatic or mildly symptomatic children. At one month follow-up, no statistically significant difference between the RV1 and placebo arms for rotavirus diarrhoea was reported (100 participants, one trial; Analysis 1.35).

One efficacy trial, RV1 Madhi 2010-AF, included children who were infected with HIV or children that have been exposed to HIV, as long as they were not clinically immunosuppressed (eg AIDS) at the age of vaccination (six weeks). HIV tests were performed in approximately 46% of children from Malawi and 23% of children from South Africa. Specific analysis for this population was not conducted, but the authors stated that demographic characteristics and the proportion of children who were infected with HIV were similar across the study groups.

1.5.4. Premature babies

One trial (RV1 Omenaca 2012-EU) included only prematurely born infants.

Serious adverse events

RV1 Omenaca 2012-EU included only prematurely born infants. There was no statistically significant difference between children that received RV1 and those that received placebo for serious adverse events (1009 participants, Analysis 1.36).

1.5.5. Breast fed or formula fed children

Feeding practices of infants in one trial (RV1 Vesikari 2007a-EU) were recorded as breast fed for at least one dose or exclusively formula fed.

Rotavirus diarrhoea: severe

At up to two years follow-up, RV1 compared to placebo reduced severe rotavirus diarrhoea in breast fed children by 91% (RR 0.09, 95% CI 0.06 to 0.14; 3046 participants, one trial), and by 98% (RR 0.02, 95% CI 0.00 to 0.14; 828 participants, one trial) in formula fed children; see Analysis 1.37.

1.6 Sensitivity analysis

1.6.1 Primary outcomes with high heterogeneity according to allocation concealment

To investigate heterogeneity for primary outcomes with pooled results where I^2 > 75%, we pooled data only from studies with good allocation concealment. There was no significant change to RR and 95% CI for these outcomes, and heterogeneity remained high, see Analysis 1.38.

Summary of findings

Summary of findings of primary outcomes according to country mortality rate (WHO strata A-E) are presented in Summary of findings for the main comparison (RV1, low-mortality countries), and in Summary of findings 2 (RV1, high-mortality countries).

2. RV5

2.1. Primary outcomes

2.1.1. Rotavirus diarrhoea: severe

Six trials provided data regarding the efficacy of RV5 to prevent severe rotavirus diarrhoea in children; see Analysis 2.1 for one year follow-up and Analysis 2.2 for two years follow-up. Trials were performed in low-mortality countries (RV5 Clark 2004-USA; RV5 Vesikari 2006b-INT; RV5 Block 2007-EU/USA; RV5 NCT00718237 2010-JPN), one trial was split between low-mortality Vietnam in stratum B (RV5 Zaman 2010-VNM) and high-mortality Bangladesh in stratum D (RV5 Zaman 2010-BGD), and another between high-mortality Ghana and Mali in stratum D (RV5 Armah 2010-GHA; RV5 Armah 2010-MLI) and high-mortality Kenya in stratum E (RV5 Armah 2010-KEN). Data below are grouped accordingly.

Low-mortality countries (WHO strata A & B)

RV5 reduced severe rotavirus diarrhoea by 87% at one year (RR 0.13, 95% CI 0.04 to 0.45; 2344 participants, three trials) and 82% by two years (RR 0.18, 95% CI 0.07 to 0.50; 3190 participants, three trials).

High-mortality countries (WHO strata D & E)

RV5 reduced severe rotavirus diarrhoea by 57% at one year (RR 0.43, 95% CI 0.29 to 0.62; 5916 participants, two trials) and 41% by two years (RR 0.59, 95% CI 0.43 to 0.82; 5885 participants, two trials). Pooled results were significantly heterogeneous at two years follow-up (I^2 = 43%); see Analysis 2.2.

2.1.2. All-cause diarrhoea: severe

Three trials provided data regarding the efficacy of RV5 to prevent severe all-cause diarrhoea in children; see Analysis 2.3 for 1 year follow-up and Analysis 2.4 for two years follow-up. Trials were performed in a low-mortality country (RV5 Vesikari 2006a-FIN), and in high-mortality countries (RV5 Armah 2010-GHA; RV5 Armah 2010-KEN; RV5 Armah 2010-MLI; RV5 Zaman 2010-AS).

Low-mortality countries (WHO stratum A)

A single trial showed a reduction in the number of severe cases of diarrhoea with RV5 compared to placebo at one year by 72% (RR 0.28, 95% CI 0.16 to 0.48; 1029 participants, one trial). This trial was conducted in Finland (RV5 Vesikari 2006a-FIN) and reported this outcome for only 53% of the enrolled patients. At the two year follow-up, there was a 96% reduction with RV5 compared to placebo (RR 0.04, 95% CI 0.00 to 0.70; 1029 participants, one trial). However, this large reduction is unlikely as the reduction for severe rotavirus diarrhoea was smaller (Analysis 2.2). It was probably a matter of chance as the sample size for this study was small and different studies reported on severe rotavirus diarrhoea.

High-mortality countries (WHO strata D & E)

There was no statistically significant difference between RV5 and placebo for all-cause severe diarrhoea at one year follow-up (4085 participants, three trials). At two years follow-up, RV5 reduced severe cases by 15% (RR 0.85, 95% CI 0.75 to 0.98; 5977 participants, four trials). Pooled results were significantly heterogeneous at one year follow-up (I^2 = 46%); see Analysis 2.3.

2.1.3. All-cause death

Nine trials reported on all-cause death, in most trials as the number of deaths (RV5 Merck[009] 2005-USA; RV5 Vesikari 2006a-FIN; RV5 Vesikari 2006b-INT; RV5 Armah 2010-AF; RV5 NCT00953056 2010-CHI; RV5 NCT00718237 2010-JPN; RV5 Zaman 2010-AS), and in two trials as fatal serious adverse events (RV5 Block 2007-EU/USA; RV5 Ciarlet 2009-EU). Number of deaths and fatal serious adverse events were pooled; see Analysis 2.5. Details of causes of death for each trial are presented in Appendix 9. Most trials were performed in low-mortality countries, one trial was split between low-mortality Vietnam in stratum B (RV5 Zaman 2010-VNM) and high-mortality Bangladesh in stratum D (RV5 Zaman 2010-BGD), and another between high-mortality Ghana and Mali in stratum D (RV5 Armah 2010-GHA; RV5 Armah 2010-MLI) and high-mortality Kenya in stratum E (RV5 Armah 2010-KEN).

Low-mortality countries (WHO strata A & B)

There was no statistically significant difference in all-cause death between RV5 and placebo arm (73,603 participants, eight trials; Analysis 2.5).

High-mortality countries (WHO strata D & E)

There was no statistically significant difference in all-cause death between the two arms (6604 participants, four trials; Analysis 2.5).

2.1.4. All serious adverse events

Serious adverse events were reported in eight trials, and performed in low-mortality countries (RV5 Vesikari 2006b-INT; RV5 Block 2007-EU/USA; RV5 Kim 2008-KOR; RV5 Ciarlet 2009-EU; RV5 NCT00953056 2010-CHI; RV5 NCT00718237 2010-JPN; RV5 Zaman 2010-VNM), and in high-mortality countries (RV5 Armah 2010-GHA; RV5 Armah 2010-KEN; RV5 Armah 2010-MLI; RV5 Zaman 2010-BGD); see Analysis 2.6.

Low-mortality countries (WHO strata A & B)

Pooled results showed no statistically significant difference in the number of serious adverse events in the RV5 group compared with the placebo group (RR 0.92, 95% CI 0.84 to 1.01; 71,638 participants, seven trials; Analysis 2.6).

High-mortality countries (WHO strata D & E)

Pooled results showed no statistically significant difference in the number of serious adverse events in the RV5 group compared with the placebo group (RR 0.93, 95% CI 0.66 to 1.33; 6588 participants, four trials; Analysis 2.6).

2.1.5. Serious adverse events: intussusception

All twelve trials reported cases of intussusception. Trials were performed in low-mortality countries (RV5 Clark 2003-USA; RV5 Clark 2004-USA; RV5 Merck[009] 2005-USA; RV5 Vesikari 2006a-FIN; RV5 Vesikari 2006b-INT; RV5 Block

2007-EU/USA; RV5 Kim 2008-KOR; RV5 Ciarlet 2009-EU; RV5 NCT00953056 2010-CHI; RV5 NCT00718237 2010-JPN; RV5 Zaman 2010-VNM), and in high-mortality countries (RV5 Armah 2010-GHA; RV5 Armah 2010-KEN; RV5 Armah 2010-MLI; RV5 Zaman 2010-BGD); see Analysis 2.7.

Low-mortality countries (WHO strata A & B)

Fourteen cases of intussusception were reported in a total of 38,321 children in the RV5 arm compared with 20 cases of intussusception in 36,553 children in the placebo arm. Pooled results showed no increased risk of intussusception in children receiving RV5 when compared to placebo (RR 0.67, 95% CI 0.34 to 1.31; 74,874 participants, 11 trials; Analysis 2.7).

High-mortality countries (WHO strata D & E)

There were no reported cases of intussusception in a total of 3294 children in the RV5 arm and 3294 children in the placebo arm (two trials).

2.2. Secondary outcomes

2.2.1. Rotavirus diarrhoea: of any severity

Seven trials provided data regarding the efficacy of RV5 to prevent rotavirus diarrhoea of any severity in children; see Analysis 2.8 for one year follow-up and Analysis 2.9 for two years follow-up. Trials were performed in low-mortality countries (RV5 Clark 2003-USA; RV5 Clark 2004-USA; RV5 Vesikari 2006b-INT; RV5 Block 2007-EU/USA; RV5 NCT00718237 2010-JPN), and in high-mortality countries (RV5 Armah 2010-GHA; RV5 Armah 2010-KEN; RV5 Armah 2010-MLI; RV5 Zaman 2010-AS). Data below are grouped accordingly.

Low-mortality countries (WHO strata A & B)

RV5 reduced the number of cases of rotavirus diarrhoea by 73% at one year (RR 0.27, 95% CI 0.22 to 0.33; 7614 participants, four trials; Analysis 2.8) and 64% during the second year (RR 0.36, 95% CI 0.25 to 0.50; 2280 participants, two trials; Analysis 2.9).

High-mortality countries (WHO strata D & E)

RV5 reduced the number of cases of rotavirus diarrhoea by 48% at one year (RR 0.52, 95% CI 0.28 to 0.94; 4806 participants, three trials; Analysis 2.8) and 39% during the second year (RR 0.61, 95% CI 0.45 to 0.83; 6744 participants, four trials; Analysis 2.9). Pooled results were significantly heterogenous at one year (I^2 = 67%; see Analysis 2.8) and at two years (I^2 = 69%; see Analysis 2.9) years follow-up.

2.2.2. All-cause diarrhoea: of any severity

One trial performed in low-mortality Finland (RV5 Vesikari 2006a-FIN), and one trial in high-mortality Kenya (RV5 Armah 2010-KEN) provided data regarding the efficacy of RV5 to prevent all-cause diarrhoea of any severity; see Analysis 2.10 for one year and Analysis 2.11 for two years follow-up.

Low-mortality countries (WHO strata A & B)

RV5 reduced the number of cases of all-cause diarrhoea by 59% at one year follow-up (RR 0.41, 95% CI 0.28 to 0.60; 1030 participants, one trial; Analysis 2.10).

High-mortality countries (WHO stratum E)

There was no statistically significant difference between RV5 and placebo for any severity all-cause diarrhoea at one year (1059 participants, one trial; Analysis 2.10) or at two years (1059 participants, one trial; Analysis 2.10) follow-up.

2.2.3. Rotavirus diarrhoea: requiring hospitalization or medical attention

RV5 reduced hospitalizations due to rotavirus diarrhoea episodes by 96% at one year of follow-up (RR 0.04, 95% CI 0.02 to 0.10; 57,134 participants, one trial; Analysis 2.12).
RV5 reduced the number of children requiring medical attention at one year of follow-up by 93% compared to placebo (RR 0.07, 95% CI 0.04 to 0.12; 57,134 participants, one trial; Analysis 2.13).
Data regarding medical attention and hospitalization rates due to all-cause diarrhoea were not estimable.

2.2.4. Reactogenicity

The incidences of fever (Analysis 2.14), diarrhoea (Analysis 2.15), and vomiting (Analysis 2.16) were evaluated after the first dose, second dose, and third dose, and at the end of the follow-up period. There was a 28% increase in the incidence of fever after the first dose of RV5 vaccine compared to placebo (RR 1.28, 95% CI 1.04 to 1.58; 3090 participants, three trials; Analysis 2.14). No statistically significant differences were observed between the RV5 and placebo groups for the other reactogenicity outcomes and timepoints. Significant heterogeneity was observed for the pooled end of follow-up data on fever (I^2 = 52%).

2.2.5. Adverse events that require discontinuation of vaccination schedule

Nine trials reported the number of adverse events leading to discontinuation of the vaccination schedule, and, overall, there was no statistically significant difference between RV5 and placebo (11,437 participants, nine trials; Analysis 2.17).

2.3. Immunogenicity

RV5 is an immunogenic vaccine and immunogenicity was measured by rotavirus vaccine virus shedding (three trials, Analysis 2.18) and seroconversion (eight trials, Analysis 2.19) after the third vaccine dose. Data, however, could not be pooled because of significant heterogeneity (I^2 = 80% and 88%, respectively).

2.4. Drop-outs before the end of trial

Similar numbers of children taking RV5 or placebo dropped out from trials before they ended (81,573 participants, 10 trials; Analysis 2.20).

2.5. Subgroup analyses

2.5.1. G type

Rotavirus diarrhoea: of any severity

When the analyses were stratified by the G type (Analysis 2.21), there were fewer episodes of rotavirus diarrhoea in the RV5 group compared to the placebo group for the G1 type (RR 0.26, 95% CI 0.21 to 0.33; 7158 participants, three trials) and the G2 type (RR 0.37, 95% CI 0.16 to 0.88; 6043 participants, two trials). The results were not statistically significant for G3 (7158 participants, three trials), G4 (6043 participants, two trials), and G9 (5673 participants, one trial).

Rotavirus diarrhoea: severe

Two trials analysed severe cases of rotavirus diarrhoea by G type (RV5 Vesikari 2006b-INT; RV5 Armah 2010-AF; Analysis 2.22).There were significantly fewer severe episodes of rotavirus diarrhoea in the RV5 groups for G4 (RR 0.11, 95% CI 0.03 to 0.48; 72,743 participants, two trials). Pooled results were not significant, but heterogenous for G1 (I^2 = 99%), G2 (I^2 = 63%), G3 (I^2 = 53%) and for G9 (I^2 = 55%).

2.5.2. HIV-infected children

One trial (RV5 Armah 2010-AF) performed HIV tests for 89% of participants and reported outcomes for HIV-infected children (38/1158); see Analysis 2.23.

Rotavirus diarrhoea: severe (up to two years follow-up)

1/21 children in the vaccine arm, and 0/17 children in the placebo arm had severe rotavirus diarrhoea during two years follow-up; there was no statistically significant difference detected between the two treatment arms.

All-cause diarrhoea: severe (up to two years follow-up)

5/21 children in the vaccine arm, and 1/17 children in the placebo arm had severe all-cause diarrhoea during two years follow-up; there was no statistically significant difference detected between the two treatment arms.

All-cause death

8/21 children in the vaccine arm, and 4/17 children in the placebo arm died; there was no statistically significant difference between the two arms.

Serious adverse events (1-14 days after any dose)

5/21 children in the vaccine arm, and 2/16 children in the placebo arm had a serious adverse event between one to 14 days after any dose; there was no statistically significant difference between the two arms.

2.5.3. Premature babies

Rotavirus diarrhoea: of any severity

In one of the included trials, RV5 Vesikari 2006b-INT, data were provided separately as the number of cases of rotavirus diarrhoea in a subgroup of 170 premature babies. RV5 was marginally better than placebo at one year follow-up (RR 0.39, 95% CI 0.15 to 1.06; Analysis 2.24) in preventing rotavirus diarrhoea for this subgroup of premature babies.

2.6 Sensitivity analysis

2.6.1 Primary outcomes with high heterogeneity according to allocation concealment

There were no primary outcomes with high heterogeneity (I^2 > 75%).

Summary of findings

Summary of findings of primary outcomes according to country mortality rate (WHO strata A-E) are presented in Summary of findings 3 (RV5, low-mortality countries), and in Summary of findings 4 (RV5, high-mortality countries).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Patient or population: children
Settings: high-mortality countries (WHO strata D & E)
Intervention: RV1
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	RV1				
Severe rotavirus diarrhoea Follow-up: up to 1 year	**50 per 1000**	**18 per 1000** (9 to 37)	**RR 0.37** (0.18 to 0.75)	5414 (2 studies)	⊕⊕⊕◯ **moderate**[1]	We did not downgrade for inconsistency as the heterogeneity observed in the pooled data (I^2 = 70%) was due to within study heterogeneity (RV1 Madhi 2010-AF results split per country).
Severe rotavirus diarrhoea Follow-up: up to 2 years	**74 per 1000**	**43 per 1000** (31 to 59)	**RR 0.58** (0.42 to 0.79)	2764 (1 study)	⊕⊕⊕◯ **moderate**[1]	
Severe all-cause diarrhoea Follow-up: up to 1 year	**137 per 1000**	**90 per 1000** (60 to 134)	**RR 0.66** (0.44 to 0.98)	4939 (1 study)	⊕⊕⊕◯ **moderate**[1]	We did not downgrade for inconsistency as the heterogeneity observed in the pooled data (I^2 = 82%) was due to within study heterogeneity (RV1 Madhi 2010-AF results split per country).

Severe all-cause diarrhoea Follow-up: up to 2 years	**233 per 1000**	**191 per 1000** (166 to 222)	**RR 0.82** (0.71 to 0.95)	2764 (1 study)	⊕⊕⊕○ **moderate**[1]
All-cause death Follow-up: 2 months to 2 years	**24 per 1000**	**21 per 1000** (16 to 30)	**RR 0.88** (0.64 to 1.22)	7481 (7 studies)	⊕⊕○○ **low**[2]
All serious adverse events Follow-up: 2 months to 2 years	**95 per 1000**	**84 per 1000** (72 to 99)	**RR 0.89** (0.76 to 1.04)	7481 (7 studies)	⊕⊕⊕○ **moderate**[3]
Serious adverse events: intussusception Follow-up: 2 months to 2 years	**0 per 100,000**	**0 per 100,000** (0 to 0)	**RR 1.49** (0.06 to 36.63)	5414 (2 studies)	⊕○○○ **very low**[1,4]

*The basis for the **assumed risk** is the control group risk across studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High-quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate-quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low-quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low-quality: we are very uncertain about the estimate.

[1] Downgraded by 1 for indirectness. Trials were conducted in Malawi and South Africa, generalisation to any high-mortality country is difficult.
[2] Downgraded by 2 for imprecision. These trials were not powered to detect an effect on mortality.
[3] Downgraded by 1 for risk of bias. Six of the seven included studies did not adequately report allocation concealment, four did not adequately report blinding, and two attrition.
[4] Downgraded by 2 for imprecision. There was a 1:10,000 increased risk of intussusception with a previous rotavirus vaccine (http://www.who.int/vaccines-documents/DocsPDF04/wwwSOWV E.pdf), therefore, these trials were not powered to detect an association between RV1 and intussusception.

Patient or population: children
Settings: low-mortality countries (WHO strata A & B)
Intervention: RV5
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	RV5				
Severe rotavirus diarrhoea Follow-up: up to 1 year	**18 per 1000**	**2 per 1000** (1 to 8)	**RR 0.13** (0.04 to 0.45)	2344 (3 studies)	⊕⊕⊕◯ **moderate**[1]	
Severe rotavirus diarrhoea Follow-up: up to 2 years	**27 per 1000**	**5 per 1000** (2 to 13)	**RR 0.18** (0.07 to 0.5)	3190 (3 studies)	⊕⊕⊕◯ **moderate**[1]	
Severe all-cause diarrhoea Follow-up: up to 1 year	**107 per 1000**	**30 per 1000** (17 to 51)	**RR 0.28** (0.16 to 0.48)	1029 (1 study)	⊕⊕◯◯ **low**[1,2]	Although the included study was conducted in only one country (Finland), we did not downgrade for indirectness as we think it is representative of low-mortality countries
Severe all-cause diarrhoea Follow-up: up to 2 years	**15 per 1000**	**1 per 1000** (0 to 11)	**RR 0.04** (0 to 0.7)	1029 (1 study)	⊕⊕◯◯ **low**[1,2]	Although the included study was conducted in only one country (Finland), we did not downgrade for indirectness as we think it is representative of low-mortality countries

All-cause death Follow-up: 2 months to 2 years	**6 per 10,000**	**7 per 10,000** (4 to 12)	**RR 1.18** (0.67 to 2.08)	73,603 (8 studies)	⊕⊕◯◯ **low**[3]
All serious adverse events Follow-up: 2 months to 2 years	**26 per 1000**	**24 per 1000** (21 to 26)	**RR 0.92** (0.84 to 1.01)	71,638 (7 studies)	⊕⊕⊕⊕ **high**
Serious adverse events: intussusception Follow-up: 2 months to 2 years	**55 per 100,000**	**37 per 100,000** (19 to 72)	**RR 0.67** (0.34 to 1.31)	74,874 (11 studies)	⊕⊕◯◯ **low**[4]

*The basis for the **assumed risk** is the control group risk across studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High-quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate-quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low-quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low-quality: we are very uncertain about the estimate.

[1] Downgraded by 1 for imprecision. The total number of events was very low.
[2] Downgraded by 1 for risk of bias. The included study did not sufficiently report incomplete outcome data.
[3] Downgraded by 2 for imprecision. These trials were not powered to detect an effect on mortality.
[4]Downgraded by 2 for imprecision. There was a 1:10,000 increased risk of intussusception with a previous rotavirus vaccine (http://www.who.int/vaccines-documents/DocsPDF04/wwwSOWV E.pdf), therefore, these trials were not powered to detect an association between RV1 and intussusception.

Patient or population: children
Settings: high-mortality countries (WHO strata D & E)
Intervention: RV5
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	RV5				
Severe rotavirus diarrhoea Follow-up: up to 1 year	**30 per 1000**	**13 per 1000** (9 to 19)	**RR 0.43** (0.29 to 0.62)	5916 (2 studies)	⊕⊕⊕⊕ **high**	
Severe rotavirus diarrhoea Follow-up: up to 2 years	**63 per 1000**	**37 per 1000** (27 to 51)	**RR 0.59** (0.43 to 0.82)	5885 (2 studies)	⊕⊕⊕⊕ **high**	
Severe all-cause diarrhoea Follow-up: up to 1 year	**77 per 1000**	**62 per 1000** (45 to 85)	**RR 0.8** (0.58 to 1.11)	4085 (1 study)	⊕⊕⊕◯ **moderate**[1]	
Severe all-cause diarrhoea Follow-up: up to 2 years	**130 per 1000**	**110 per 1000** (97 to 127)	**RR 0.85** (0.75 to 0.98)	5977 (2 studies)	⊕⊕⊕⊕ **high**	
All-cause death Follow-up: 2 months to 2 years	**26 per 1000**	**24 per 1000** (18 to 32)	**RR 0.93** (0.69 to 1.25)	6604 (2 studies)	⊕⊕◯◯ **low**[2]	
All serious adverse events Follow-up: 2 months to 2 years	**19 per 1000**	**18 per 1000** (12 to 25)	**RR 0.93** (0.66 to 1.33)	6588 (2 studies)	⊕⊕⊕◯ **moderate**[3]	

Serious adverse events: intussusception Follow-up: 2 months to 2 years	See comment	See comment	Not estimable	6588 (2 studies)	⊕⊕◯◯ **low**[4]	No events were reported.

*The basis for the **assumed risk** is the control group risk across studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High-quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate-quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low-quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low-quality: we are very uncertain about the estimate.

[1] Downgraded by 1 for indirectness. Single trial conducted in three African countries (Mali, Ghana, and Kenya), generalisation to any high-mortality country is difficult.
[2] Downgraded by 2 for imprecision. These trials were not powered to detect an effect on mortality.
[3] Downgraded by 1 for imprecision. The 95% CI includes both no effect and appreciable harm.
[4] Downgraded by 2 for imprecision. There was a 1:10,000 increased risk of intussusception with a previous rotavirus vaccine (http://www.who.int/vaccines-documents/DocsPDF04/wwwSOWV E.pdf), therefore, these trials were not powered to detect an association between RV1 and intussusception.

DISCUSSION

Rotavirus vaccines have been under development since the 1980s, and four have been approved for use. RRV-TV (Rotashield) has not been used since 1999. RV1, RV5, and LLR are in use today and are the focus of this review.

Summary of main results

Forty-one trials were included with 186,263 participants, evaluating RV1 (29 trials) and RV5 (12 trials); none of the trials assessed LLR. Our analysis stratified the primary outcomes by WHO mortality strata (high-mortality countries, with high child mortality; and low-mortality, with low child mortality; WHO 1999).
Trials were not designed or powered to detect an effect on preventing death or on the occurrence of possible severe adverse effects, such as intussusception.

1. RV1 in countries with low child mortality (WHO strata A and B)

Eight trials were conducted in Asia, five in Europe, four in Latin America, four in North America, and one in Europe and Latin America.

In infants under one year

RV1 prevents 86% of cases of severe rotavirus diarrhoea: RR 0.14, 95% CI 0.07 to 0.26; 40,631 participants, six trials; moderate-quality evidence.
RV1 prevents 40% of severe all-cause diarrhoea episodes: Rate ratio 0.60, 95% CI 0.50 to 0.72; 17,867 participants, one trial; moderate-quality evidence.

In children up to two years

RV1 prevents 85% of cases of severe rotavirus diarrhoea: RR 0.15, 95% CI 0.12 to 0.20; 32,854 participants, eight trials; high-quality evidence.
RV1 prevents 37% of severe all-cause diarrhoea episodes: Rate ratio 0.63, 95% CI 0.56 to 0.71; 39,091 participants, two trials; moderate-quality evidence.
For all cause death, an effect of the vaccine has not been shown: RR 1.27, 95% CI 0.89 to 1.81; 93,321 participants, 18 trials; low-quality evidence.
For serious adverse events, children receiving RV1 had 10% fewer events than those receiving placebo: RR 0.90, 95% CI 0.84 to 0.95; 91,957 participants, 20 trials; moderate-quality evidence.
For intussusception, RV1 was not associated with a higher risk: RR 0.87, 95% CI 0.52 to 1.46; 91,832 participants, 11 trials; low-quality evidence.
See Summary of findings for the main comparison.

2. RV1 in countries with high child mortality (WHO strata D and E)

One trial was conducted in Bangladesh, one in India, one in Peru, three in South Africa, and one in South Africa and Malawi.

In infants under one year

RV1 prevents 63% of cases of severe rotavirus diarrhoea: RR 0.37, 95% CI 0.18 to 0.75; 5414 participants, two trials; moderate-quality evidence.
RV1 prevents 34% of severe all-cause diarrhoea episodes: RR 0.66, 95% CI 0.44 to 0.98; 4939 participants, one trial; moderate-quality evidence.

In children up to two years

RV1 prevents 42% of cases of severe rotavirus diarrhoea: RR 0.58, 95% CI 0.42 to 0.79; 2764 participants, one trial; moderate-quality evidence.
RV1 prevents 18% of severe all-cause diarrhoea episodes: RR 0.82, 95% CI 0.71 to 0.95; 2764 participants, one trial; moderate-quality evidence.
For all-cause death, an effect of the vaccine has not been shown: RR 0.88, 95% CI 0.64 to 1.22; 7481 participants, seven trials; low-quality evidence.
For serious adverse events, an effect of the vaccine has not been shown: RR 0.89, 95% CI 0.76 to 1.04; 7481 participants, seven trials; moderate-quality evidence.
For intussception, RV1 was not associated with a higher risk: RR 1.49, 95% CI 0.06 to 36.63; 5414 participants, two trials; very low-quality evidence.
See Summary of findings 2.

3. RV5 in countries with low child mortality (WHO strata A and B)

Four trials were conducted in Asia, two in Europe, three in North America, one in Europe and the USA, and one in Europe and the Americas.

In infants under one year

RV5 prevents 87% of cases of severe rotavirus diarrhoea: RR 0.13, 95% CI 0.04 to 0.45; 2344 participants, three trials; moderate-quality evidence.
RV5 prevents 72% of severe all-cause diarrhoea episodes: RR 0.28, 95% CI 0.16 to 0.48; 1029 participants, one trial; low-quality evidence.

In children up to two years

RV5 prevents 82% of cases of severe rotavirus diarrhoea: RR 0.18, 95% CI 0.07 to 0.50; 3190 participants, three trials; moderate-quality evidence.

RV5 prevents 96% of severe all-cause diarrhoea episodes: RR 0.04, 95% CI 0.00 to 0.70; 1029 participants, one trial; low-quality evidence.

For all cause death, an effect of the vaccine has not been shown: RR 1.18, 95% CI 0.67 to 2.08; 73,603 participants, eight trials; low-quality evidence.

For serious adverse events, an effect of the vaccine has not been shown: RR 0.92, 95% CI 0.84 to 1.01; 71,638 participants, seven trials; high-quality evidence.

For intussception, RV5 was not associated with a higher risk: RR 0.67, 95% CI 0.34 to 1.31; 74,874 participants, 11 trials; low-quality evidence.

See Summary of findings 3.

4. RV5 in countries with high child mortality (WHO strata D and E)

One trial was conducted in Ghana, Kenya and Mali, and one trial in Bangladesh and Vietnam.

In infants under one year

RV5 prevents 57% of cases of severe rotavirus diarrhoea: RR 0.43, 95% CI 0.29 to 0.62; 5916 participants, two trials; high-quality evidence.

Data on all-cause diarrhoea was reported in one trial. This suggested a protective effect, but the results were not statistically significant: RR 0.80, 95% CI 0.58 to 1.11; 4085 participants, one trial; moderate-quality evidence.

In children up to two years

RV5 prevents 41% of cases of severe rotavirus diarrhoea: RR 0.59, 95% CI 0.43 to 0.82; 5885 participants, two trials; high-quality evidence.

RV5 prevents 15% of severe all-cause diarrhoea episodes: RR 0.85, 95% CI 0.75 to 0.98; 5977 participants, two trials; high-quality evidence.

For all cause death, an effect of the vaccine has not been shown: RR 0.93, 95% CI 0.69 to 1.25; 6604 participants, two trials; low-quality evidence.

For serious adverse events, an effect of the vaccine has not been shown: RR 0.93, 95% CI 0.66 to 1.33; 6588 participants, two trials; moderate-quality evidence.

For intussception, RV5 was not associated with a higher risk: no cases were reported, 6588 participants, two trials; low-quality evidence.

See Summary of findings 4.

Children in trials performed in low-mortality countries received the vaccines according to the country's immunization schedule. For trials of RV1 conducted in high-mortality Malawi, South Africa, and Bangladesh (RV1 Zaman 2009-BGD; RV1 Madhi 2010-AF; RV1 Steele 2010b-ZAF) children received the first dose of the vaccine at a later age (10 to 12 weeks) than is recommended in the EPI schedule (six weeks).

Overall completeness and applicability of evidence

We carried out this systematic review using RCTs. All the included trials were placebo controlled, which meant there were no data directly comparing RV1 with RV5. Furthermore, potential herd protection afforded by vaccination could not be evaluated. We did not identify any RCTs for LLR, although case-control studies have demonstrated a vaccine effectiveness for LLR of 77% (Fu 2010). The trials provided only limited data for special groups of children, such as preterm infants, malnourished children, and immunocompromised children.

Country mortality rate

Trials of RV1 and RV5 in high-mortality countries in Africa and Asia demonstrated a lower vaccine efficacy when compared to trials performed in low-mortality countries. Despite the lower efficacy in high-mortality countries, because of the higher burden of rotavirus disease, the absolute number of events prevented by vaccination is greater (RV1 Madhi 2010-AF). The reasons for a reduced efficacy in high-mortality countries is not known, but is a feature shared with other live, oral vaccines; factors could include higher levels of passively transferred maternal antibody, concurrent administration of oral polio vaccine (OPV), breastfeeding, malnutrition, and enteric co-infections (Cunliffe 2007; Patel 2009; Levine 2010).

Reduced efficacy in high-mortality countries in trials reporting two years of follow-up could be explained by waning vaccine-induced immunity, or some protection in the placebo group resulting from natural rotavirus infection (RV1 Madhi 2010-AF). Rotavirus diarrhoea is particularly associated with severe outcomes between the ages of three and 35 months of age (Parashar 2006b), with a peak incidence of all episodes occurring between six and 24 months (CDC-ASIP 1999; Linhares 2008). Protection afforded by vaccination should therefore extend to at least two years of age.

Schedule and age

Trials performed in high-mortality countries examined the efficacy of RV1 when administered at 10 to 14 weeks of age. It is uncertain whether the vaccine would perform equally well in high-mortality settings if given at six to 10 weeks of age, because of potential interference by maternal antibodies and the first dose of OPV.

All-cause diarrhoea

The impact of rotavirus vaccination on severe all-cause diarrhoea from a public health perspective is important as laboratories in low-income countries may not routinely test for rotavirus infection, and parents and care-givers are particularly concerned about severe cases of diarrhoea (Mast 2009). Surprisingly, few trials reported vaccine efficacy against all-cause diarrhoea. In addition, it should be noted that vaccine efficacy against less severe all-cause diarrhoea is lower, meaning that vaccination may not have a noticeable impact on milder episodes of diarrhoea occurring in the community.

Mortality data

The included trials were not individually powered to detect a mortality effect. This review did not detect a difference in the number of deaths for children receiving any of the vaccines or placebo. Furthermore, many studies were conducted in low-mortality countries where deaths from diarrhoea are rare. Two recent post-vaccine implementation national surveillance studies from Mexico and Brazil reported that the introduction of RV1 into the national immunization programme was associated with a decline in the number of diarrhoea-related deaths (Richardson 2010; do Carmo 2011) in comparison with historical controls.

Safety data

There was no detectable difference in the number of cases of intussusception for children receiving vaccine or placebo. Although post-introduction safety surveillance in Mexico, Brazil, and Australia reported an increased risk of intussusception within a week of administration of the first or second vaccine dose of RV1 (Patel 2011) and RV5 (Buttery 2011), the association between all live, oral rotavirus vaccines, and intussusception is debatable. Overall the risk/benefit analyses in high rotavirus disease burden countries favours vaccination (Patel 2011).

Quality of the evidence

The trials included in the current review were all placebo-controlled, were conducted in Latin America, North America, Europe, Asia, and Africa, and the largest included over 60,000 children; the need for such trials was identified in the original version of the review (Soares-Weiser 2004). However, most children were followed for safety outcomes only. The reporting of trial methods was poor in many trials and often we could not adequately assess the risk of bias in the trials. In particular, only 61% of the included trials reported an adequate generation of allocation sequence and only 46% described the methods used to conceal allocation. We have sought to obtain this information from trialists and received detailed information about the design of studies for most of the RV5 trials. However, up to the publication of the current update, we have not yet received information from GSK on the RV1 trials. This impacted upon the risk of bias assessments and summary of findings (see below).

Potential biases in the review process

As can be seen in the summary of findings tables, the quality of evidence for some of the primary outcomes in this review were downgraded because the primary studies did not adequately report details of randomization procedure, allocation concealment, and procedures to avoid attrition and selection bias. By downgrading the quality of the evidence, we may have introduced bias.

Agreements and disagreements with other studies or reviews

We identified three systematic reviews of RCTs that have been conducted since the 2010 update of this Cochrane systematic review: two evaluated severe episodes of rotavirus diarrhoea and mortality (Munos 2010; Fischer Walker 2011); and the third attempted to infer the outstanding challenges of vaccine implementation in low-income countries (Ustrup 2011). There was little overlap between the scope of these reviews and the current review.

Relationship to current policies

The data in this review support the WHO's Strategic Advisory Group of Experts (SAGE) on Immunization's recommendation for "the inclusion of rotavirus vaccination of infants into all national immunization programmes" with a stronger recommendation for countries where "diarrhoeal deaths account for ≥10% of mortality among children aged <5 years" (SAGE 2009).
A two-dose (6 & 10 week) RV1 schedule recommended by WHO has not been examined in an efficacy trial.

AUTHORS' CONCLUSIONS

Implications for practice

- RV1 and RV5 are efficacious vaccines in preventing rotavirus diarrhoea with comparable safety and efficacy profiles. The systematic review data support the global WHO rotavirus vaccine recommendation (SAGE 2009; SAGE 2012).

- The data from the included RCTs exclude a risk of intussusception with RV1 and RV5 of the magnitude observed with the first licensed vaccine (RRV-TV, RotaShield). However, since the data cannot exclude a smaller risk of intussusception or other rare serious adverse events, routine vaccine introduction

should be accompanied by safety surveillance (Buttery 2011; Patel 2011).

- We did not identify any trials of LLR, which is licensed for use in China.

Implications for research

Placebo controlled efficacy trials of RV1 and RV5 have been undertaken in representative populations of low- and high-mortality countries and do not require repetition. Further research would be valuable in the following areas:

- Post-introduction studies to examine vaccine effectiveness particularly in high-mortality countries.

- A greater understanding of the lower vaccine efficacy observed in high-mortality countries in Africa and Asia in the first and second years of life.

- Since the recommended two-dose RV1 schedule at the age of six and 10 weeks may be less efficacious than the two-dose schedule examined at 10 and 14 weeks of age in clinical trials in Africa (eg because of higher levels of maternal antibody and concurrent administration of the first dose of OPV), vaccine effectiveness with the 6 and 10 week schedule should be evaluated following RV1 roll-out in EPI.

- Studies to assess the potential benefit of alternative dosage schedules of rotavirus vaccine especially in high-mortality countries (eg neonatal dosing, later dosing, additional dosing).

- Further information on rotavirus vaccine efficacy in special populations.

- Post-introduction studies in representative countries should examine vaccine safety with particular respect to intussusception and analyse the risk/benefit of rotavirus vaccination (Patel 2011). Given the rareness of the event, data from different countries may need to be pooled.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

RV1 Anh 2011-PHL

Methods	RCT **Length of follow-up:** 1 month after last dose **Adverse event data collection methods:** not reported
Participants	**Number:** 375 enrolled; ATP safety cohort: 345; ATP immunogenicity cohort: 292 **Inclusion criteria:** healthy infants aged 5-10 weeks at the time of the first study vaccination dose with a birth weight of >2 kg **Exclusion criteria:** use of any investigational drug or vaccine other than the study vaccine or confirmed immunosuppression/immunodeficient conditions or allergy to RIX4414 vaccine/placebo components
Interventions	1. Two doses of RIX4414* plus one dose of placebo according to a PL-V-V schedule 2. Two doses of RIX4414* plus one dose of placebo according to a V-PL-V schedule 3. Three placebo doses * Human rotavirus [RV1] liquid vaccine, oral suspension (GSK Biologicals, Belgium), containing at least $10^{6.0}$ median Cell Culture Infective Dose 50 percent ($CCID_{50}$) of live attenuated RIX4414 human rotavirus strain (G1P[8]) **Schedule:** 3 doses according to a 0, 1, and 2 month schedule
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity, including fever, diarrhoea and vomiting, 8 days after each dose (collected from GSK report) 2. Adverse events leading to discontinuation 3. Serious adverse events 4. Fatal serious adverse events 5. Drop-outs 6. * Rotavirus diarrhoea, rotavirus antigen isolated from any of the stool samples collected from children with diarrhoea episodes, up to 1 month after last dose 7. * All-cause diarrhoea, up to 1 month after last dose **Outcomes to measure immunogenicity** 8. Anti-rotavirus IgA antibody seroconversion, $\geq$20 U/mL * Outcome reported as proportion (P) with 95% CI. Events (n) and totals (N) were estimated by using the values when two formulas for the standard error (SE) converged
Immunization status	Commercially available diphtheria, tetanus, whole-cell pertussis (DTPw), hepatitis B (HBV) and oral poliovirus (OPV) vaccines were administered concomitantly with the study vaccine/placebo as part of the routine Expanded Programme of Immunization (EPI) in the Philippines
Location	Philippines (single centre) WHO mortality stratum B

RV1 Anh 2011-PHL (*Continued*)

Notes	Study known as *RIX GSK[063] 2008-AS* in previously published versions of this review **Date:** March to September 2007 **Source of funding:** GlaxoSmithKline Biologicals **Study rationale:** "This study will provide data on the immune response and safety of GSK Biologicals' HRV [human rotavirus] liquid vaccine when given along with the routine infant immunizations in Philippines." "The study also[...]explored the potential effect of scheduling of the HRV [human rotavirus] vaccine doses with respect to the existing routine vaccination schedules"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated "Block randomization scheme (2:2:1 ratio) with standard SAS program was used"
Allocation concealment (selection bias)	Low risk	Central allocation "Based on the block size, the vaccine doses were distributed to each of the study centers"
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and key personnel were blinded "The study was double-blind with respect to the RIX4414 oral suspension (liquid formulation), placebo and scheduling of doses. The parents/guardians of infants, investigators and study personnel were unaware of the study vaccine/ placebo administered" "The placebo was identical to the vaccine in composition"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition balanced across groups with reasons for drop-out/exclusion reported
Selective reporting (reporting bias)	Low risk	All pre-published outcomes included
Other bias	Unclear risk	Funded by GlaxoSmithKline Biologicals

RV1 Anh 2011-VNM

Methods	RCT **Length of follow-up:** 1 month after last dose **Adverse event data collection methods:** not reported

Participants	**Number:** 375 enrolled; ATP safety cohort: 352; ATP immunogenicity cohort: 330 **Inclusion criteria:** healthy infants aged 6 to 10 weeks at the time of the first study vaccination dose with a birth weight of > 2 kg **Exclusion criteria:** use of any investigational drug or vaccine other than the study vaccine or confirmed immunosuppression/immunodeficient conditions or allergy to RIX4414 vaccine/placebo components
Interventions	1. Two doses of RIX4414* plus one dose of placebo according to a V-V-PL schedule 2. Two doses of RIX4414* plus one dose of placebo according to a V-PL-V schedule 3. Three placebo doses * Human rotavirus [RV1] liquid vaccine, oral suspension (GSK Biologicals, Belgium), containing at least 10^6 median Cell Culture Infective Dose 50 percent ($CCID_{50}$) of live attenuated RIX4414 human rotavirus strain (G1P[8]) **Schedule:** 3 doses according to a 0, 1, and 2 month schedule
Outcomes	**Clinical outcome measures (Safety and Efficacy)** 1. Reactogenicity, including fever, diarrhoea and vomiting, 8 days after each dose (collected from GSK report) 2. Adverse events leading to discontinuation 3. Serious adverse events 4. Fatal serious adverse events 5. Drop-outs 6. * Rotavirus diarrhoea, rotavirus antigen isolated from any of the stool samples collected from children with diarrhoea episodes, up to 1 month after last dose (outcome not included in the pre-published protocol) 7. * All-cause diarrhoea, up to 1 month after last dose (outcome not included in the pre-published protocol) **Outcomes to measure immunogenicity** 8. Anti-rotavirus IgA antibody seroconversion, ≥20 U/ML * Outcome reported as proportion (P) with 95% CI. Events (n) and totals (N) were estimated by using the values when two formulas for the standard error (SE) converged
Immunization status	Commercially available diphtheria, tetanus, whole-cell pertussis (DTPw), hepatitis B (HBV) and oral poliovirus (OPV) vaccines were administered concomitantly with the study vaccine/placebo as part of the routine Expanded Programme of Immunization (EPI) in Vietnam
Location	Vietnam (11 satellite centres) WHO mortality stratum B
Notes	Study known as *RIX GSK[051] 2008-AS* in previously published versions of this review **Date:** September 2006 to March 2007 **Source of funding:** GlaxoSmithKline Biologicals **Study rationale:** "To provide specific data on immunogenicity of GSK Biologicals' human rotavirus liquid vaccine, when co-administered with the routine Expanded Program of Immunization (EPI) in Vietnam. The study will also assess reactogenicity and safety of the human rotavirus liquid vaccine relative to the placebo"

RV1 Anh 2011-VNM (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated "Block randomization scheme (2:2:1 ratio) with standard SAS program was used"
Allocation concealment (selection bias)	Low risk	Central allocation "Based on the block size, the vaccine doses were distributed to each of the study centers"
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and key personnel were blinded. "The study was double-blind with respect to the RIX4414 oral suspension (liquid formulation), placebo and scheduling of doses. The parents/guardians of infants, investigators and study personnel were unaware of the study vaccine/ placebo administered" "The placebo was identical to the vaccine in composition"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition balanced across groups with reasons for drop-out/exclusion reported
Selective reporting (reporting bias)	Unclear risk	One outcome (rotavirus diarrhoea) not included in the pre-published protocol
Other bias	Unclear risk	Funded by GlaxoSmithKline Biologicals

RV1 Bernstein 1998-USA

Methods	RCT **Length of follow-up:** outcomes measured up to 1 month after the second dose **Adverse event data collection methods:** participants or their parents filled out a diary card for 7 days after each dose (passive method)
Participants	**Number:** 42 enrolled; 42 evaluable **Inclusion criteria:** all infants aged 6 to 26 weeks recruited from private practice offices in Cincinnati **Exclusion criteria:** not stated
Interventions	RV1 1. RIX4414 (RV1): 10^5 PFU; 21 participants 2. Placebo: 20 participants **Schedule:** 2 doses given 6 to 10 weeks apart

Outcomes	**Clinical outcome measures** 1. Reactogenicity: diarrhoea defined as > 3 stools that were looser than normal in a 24-h period; fever defined as a temperature > 100.4 °F obtained rectally in infants 2. Serious adverse events 3. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity** 4. Vaccine virus shedding: rotavirus shedding after immunization; combined time points (review includes data from combined time points) 5. Seroconversion: ≥ 4-fold rise in rotavirus IgA antibody (serum and stool) (review includes data from after dose 1 and dose 2)
Immunization status	Rotavirus vaccine was separated from all other infant vaccines by at least 2 weeks
Location	Cincinnati, USA WHO mortality stratum A
Notes	**Date:** August to November 1995 **Source of funding:** Virus Research Institute, Inc. (now Avant Immunotherapeutics Inc.) 1 participant in the placebo group did not complete the study because of persistent otitis media

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Unclear risk	Trial report does not provide enough details

RV1 Bernstein 1999-USA

Methods	RCT **Length of follow-up:** outcomes measured at 2 years **Adverse event data collection methods:** "diary card for 7 days after vaccine. All moderate to severe side effects were reported by the investigator to an independent study monitor on a continuous basis during the study" (passive method); "telephoned parents every 2 weeks after the first immunisation, and then weekly during the expected rotavirus season (Jan 1-May 31) as a reminder and to collect data on any adverse events" (active method)
Participants	**Number:** 215 randomized; 214 evaluable **Age range:** 3 to 6 months **Inclusion criteria:** healthy children aged 10 to 16 weeks at the time of the first dose **Exclusion criteria:** fever; premature labour; an immunosuppressed or pregnant individual in the same household; birth at < 36 weeks of gestation; participation in any other investigational clinical trial; or no telephone in the household
Interventions	89-12 (a precursor of RIX4414 (RV1) 1. 89-12 (a precursor of RIX4414 (RV1)): 10^5 PFU; 2 doses given 6 to 10 weeks apart; 108 participants 2. Placebo: 10^5 PFU; 2 doses given 6 to 10 weeks apart; 107 participants "Infants received an oral dose of 1.0 mL vaccine (10^5 PFU) or placebo immediately after 2.0 mL of an antacid containing 160 mg aluminium hydroxide and 160 mg magnesium hydroxide to buffer stomach acid. The infant was not fed for 1 h before or after the immunisation"
Outcomes	**Clinical outcome measures** 1. All-cause diarrhoea: gastroenteritis defined as vomiting (> 1 h after feeding), diarrhoea (≥ 3 looser than normal stools in a 24-h period), or both; measured up to 2 years 2. Severe rotavirus diarrhoea: severity assessed using a scoring system with a "20-point scale identical to that used in previous rotavirus trials. In this system, points are assigned according to the duration and severity of diarrhoea and vomiting, the severity of fever, and the presence of dehydration or hospital admissions for each episode of gastroenteritis. A score greater than 8 was prospectively defined as severe, and a score more than 14 as very severe"; measured up to 2 years 3. Rotavirus diarrhoea: "An illness was classified as caused by rotavirus if a stool specimen collected no later than 7 days after resolution of symptoms contained rotavirus antigen. All episodes of rotavirus gastroenteritis occurring between the second vaccination and the end of the study were included"; measured up to 7 days 4. Reactogenicity: "Parents filled out a diary card for 7 days after each dose. Signs included were: daily (evening) rectal temperatures, diarrhoea, vomiting, and the number and consistency of all stools"; measured up to 7 days 5. All-cause death; measured up to 2 years 6. Emergency department visit; measured up to 2 years 7. Rotavirus diarrhoea requiring hospitalization **Outcomes to measure immunogenicity** 8. Vaccine virus shedding (review includes after dose 2 data) 9. Immunogenicity (ELISA): "Serum samples were analysed for IgA and IgG antibody to rotavirus by an ELISA" and "neutralising antibody to the 89-12 strains by an antigen reduction assay" (only rotavirus-specific IgA results reported in this review from after dose 2 time point)

RV1 Bernstein 1999-USA (*Continued*)

Immunization status	Other vaccines separated from the trial vaccines by at least 2 weeks
Location	Cincinnati, Baltimore, and Sellersville, USA WHO mortality stratum A
Notes	**Date:** August 1997 to June 1998 **Source of funding:** Virus Research Institute, Inc. (now Avant Immunotherapeutics Inc.)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Infants were assigned to receive either 89-12 or placebo according to a computer-generated randomization schedule (one/one) in blocks of ten provided by the sponsor The intention-to-treat analysis included all participants who received at least one dose of study vaccine. Before the code was broken, all cases of rotavirus gastroenteritis and the severity of each episode were verified"
Allocation concealment (selection bias)	Low risk	As above
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind, no details
Incomplete outcome data (attrition bias) All outcomes	Low risk	No impact on intervention effect estimate "Of the 215 children enrolled, 213 received both doses of vaccine or placebo, and 214 were followed up for gastrointestinal disease. One child in the vaccine group did not receive the vaccine because of persistent fever at the time of the scheduled revaccination, and one child in the placebo group was found to have a congenital tracheal malformation while in the trial and was not revaccinated"
Selective reporting (reporting bias)	Low risk	All expected outcomes included
Other bias	Unclear risk	Insufficient information

RV1 Dennehy 2005-NA

Methods	RCT **Length of follow-up:** 10 to 12 months **Adverse event data collection methods:** "For the 15 days after each dose of vaccine, the parent or guardian maintained a daily record that included fever, irritability/fussiness, diarrhoea, vomiting, loss of appetite and cough/runny nose. In addition, the parent or guardian was asked to record any gastroenteritis episode occurring in the period from the first dose until 2 months after the second dose of vaccine." (passive method); "Subjects were also monitored for any serious adverse events occurring throughout participation in the study (10-12 months in total) and for unsolicited adverse events occurring within 43 days after each dose of vaccine or placebo" (active method)
Participants	**Number:** 529 enrolled; 479 evaluable **Age range:** 1 to 3 months (beginning) **Inclusion criteria:** healthy infants aged 5 to 15 weeks at the time of the first dose. Vaccine administration delayed if acute illness present (fever > 38 °C/gastroenteritis/antibiotics within 7 days before scheduled vaccination) **Exclusion criteria:** premature labour (< 36 weeks); chronic condition; (chronic gastrointestinal disease, immunosuppressive diseases); household contact with immunosuppressed individuals/pregnant women
Interventions	RV1 1. RIX4414 (RV1) 1.1. $10^{5.2}$; 212 participants 1.2. $10^{6.4}$; 209 participants 2. Placebo: 108 participants **Schedule:** 2 doses given 7 weeks apart
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity: fever, irritability/fussiness, diarrhoea, vomiting, loss of appetite and cough/runny nose; measured during 15 days post-vaccination 2. Serious adverse events 3. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity** 4. Viral shedding: viral shedding in any stool specimen collected between first dose and 2 months after second vaccine dose (review includes after dose 2 data) 5. Seroconversion: anti-rotavirus IgA ELISA $\geq$ 20 Units/mL in participants negative for rotavirus antibody before the first dose of vaccine (review includes data from 2 months after dose 2)
Immunization status	Vaccine or placebo given concomitantly with diphtheria-tetanus-acellular pertussis, inactivated poliovirus, *H. influenzae* type b, and *Streptococcus pneumoniae* conjugate vaccines for participants in USA or with a diphtheria-tetanus-acellular pertussis/inactivated poliovirus/*H. influenza* type b combination vaccine for participants in Canada "Routine hepatitis B vaccinations were administered according to local practice"
Location	41 centres in USA and Canada WHO mortality stratum A

RV1 Dennehy 2005-NA (*Continued*)

Notes	**Date:** 13 December 2000 to 2 August 2002 **Source of funding:** GlaxoSmithKline Biologicals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Low risk	Central allocation; "double blind randomized unbalanced allocation scheme (2:2:1 ratio)"
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and key personnel; "Study personnel and families were blinded to group assignment until study completion"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced across groups; "Fifty-nine subjects, who were proportionately distributed among vaccine groups, did not complete the entire 10- to 12-month study"
Selective reporting (reporting bias)	Unclear risk	No details
Other bias	Unclear risk	No details

RV1 GSK[021] 2007-PAN

Methods	RCT **Length of follow-up:** 1 month after dose 3 **Adverse event data collection methods:** not reported
Participants	**Number:** 228 enrolled; 203 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants, born after a normal gestation period of $\geq$ 36 weeks; 6 to 12 weeks of age at the time of the first dose of the study vaccination course; free of obvious health problems as established by medical history and clinical examination before entering into study **Exclusion criteria**: any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the gastrointestinal tract or other serious medical condition as determined by the investigator and previous confirmed occurrence of rotavirus gastroenteritis
Interventions	RV1 1. RIX4414 (RV1): $10^{6.5}$ PFU*; 177 participants (randomized)

	1.1 Received modified vaccine formulation 1.2 Received a licensed RV1 vaccine *Dose unclear; in the same study, some use $10^{6.5}$ PFU and some 10^{5} PFU 2. Placebo: 51 participants (randomized) 2.1 Received a placebo of the modified vaccine formulation 2.2 Received a placebo of the licensed RV1 vaccine **Schedule:** 3 doses at 2, 4, and 6 months of age
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity: for each type of solicited symptom, occurrence of the symptom within the 8-day (days 0 to 7) solicited follow-up period after each dose; occurrence of unsolicited adverse events within 31 days (days 0 to 30) after each dose, according to MedDRA classification; measured up to 31 days after vaccine/placebo 2. Serious adverse events: occurrence throughout entire study period; measured up to 31 days after vaccine/placebo 3. Drop-outs: measured up to 31 days after vaccine/placebo 4. All-cause death 5. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity** 6. Viral shedding: number (%) of participants with rotavirus in at least 1 stool (review includes data from combined time points) 7. Seroconversion: appearance of anti-rotavirus antibody concentration $\geq$ 20 U/mL in participants negative for rotavirus before vaccination (review includes data from 2 months after dose 1 and 2 months after dose 2, and 1 month after dose 3)
Immunization status	Use of other vaccines not mentioned
Location	1 centre in Panama WHO mortality stratum B
Notes	**Date:** 23 August 2002 to 9 May 2003 **Source of funding:** GlaxoSmithKline Biologicals **Study rationale:** "to compare the immunogenicity and safety of a modified vaccine formulation to the licensed human rotavirus [Rotarix] vaccine"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	No details; "treatment allocation of 7:7:1:1"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details; "Double blind with respect to human rotavirus [Rotarix] vaccine and its placebo"

RV1 GSK[021] 2007-PAN (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions
Selective reporting (reporting bias)	Unclear risk	No details
Other bias	Unclear risk	No details

RV1 GSK[024] 2008-LA

Methods	RCT **Length of follow-up:** up to 1 year of age **Adverse event data collection methods:** not reported
Participants	**Number:** 6568 enrolled; 6349 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** males or females between, and including 6 and 12 weeks (42 to 90 days) of age at the time of the first vaccination according to the country recommendations for the routine vaccination schedules; free of obvious health problems as established by medical history and clinical examination before entering into the study **Exclusion criteria:** history of chronic gastrointestinal disease including any uncorrected congenital malformation of the gastrointestinal tract or other serious medical condition as determined by the investigator
Interventions	RV1 1. RIX4414 (RV1): $10^{6.5}$ PFU; 2 doses at 1 or 2 months; 4376 participants (randomized) 2. Placebo: 2 doses at 1 or 2 months; 2192 participants (randomized) **Schedule:** both groups received RV1 vaccine or placebo vaccine orally; first dose at month 0 then second dose at month 1 or month 2 **2 cohorts:** there were two periods of enrolment, each with its own visit schedule: • Cohort enrolled in 2003 to 2004: visits 1, 2, 3, 4 (for a subset only) and 5 corresponded to month 0 (vaccine dose 1), month 1 to 2 (vaccine dose 2), month 2 to 4, month 3 to 6, and month 10 in the schedule • Cohort enrolled in 2005: visits 1, 2 (for a subset only), 3, 4 (for a subset only), 5, 6 (for a subset only), and 7 corresponded to month 0 (vaccine dose 1), month 1, month 2 (vaccine dose 2), month 3, month 4, month 5, and month 10 in the schedule
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Rotavirus diarrhoea: occurrence of severe rotavirus gastroenteritis (requiring hospitalizations and/or rehydration therapy in a medical facility) caused by the wild rotavirus strains during the period starting from 2 weeks after dose 2 until 1 year of age; measured up to 1 year after vaccine/placebo 2. Serious adverse events: occurrence of throughout the entire study period; measured up to 1 year after vaccine/placebo 3. Drop-outs: measured up to 1 year after vaccine/placebo 4. All-cause death: fatal serious adverse events; measured up to 1 year after vaccine/placebo 5. Adverse events resulting in discontinuation 6. All-cause diarrhoea - severe

	Outcomes to measure immunogenicity 7. Seroconversion: serum rotavirus immunoglobulin A (IgA) antibody concentrations 1 to 2 months after second study vaccine dose (at visit 3) in a subset of 300 subjects enrolled in year 2003-2004 (review includes data from 1 to 2 months after dose 2)
Immunization status	All participants received routine infant vaccinations (Hepatitis B vaccine), diphtheria-tetanus-acellular pertussis, poliovirus, and *H. influenzae* type b) according to Expanded Programme of Immunization (EPI) recommendations in each country First 2 doses of routine EPI vaccinations were co-administered with the RV1 vaccine or placebo doses; the third routine EPI vaccination was administered 1 to 2 months later according to the national plan of immunization in each country
Location	Multiple sites in 6 countries in Latin America (Argentina, Brazil, Colombia, Dominican Republic, Honduras, and Panama) WHO mortality stratum B
Notes	**Date:** 3 December 2003 to 20 March 2007 **Source of funding:** GlaxoSmithKline Biologicals **Study rationale:** "to evaluate the efficacy, immunogenicity and safety of 2 doses of oral live attenuated human rotavirus [RV1] vaccine given concomitantly with routine EPI vaccinations (including DTPw [licensed combined diphtheria and tetanus toxoids and whole-cell pertussis vaccine], HBV [licensed hepatitis type B vaccine], Hib [licensed *H. influenzae* type b vaccine] and OPV [oral polio vaccine]) in healthy infants"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The ATP cohort for immunogenicity included all vaccinated subjects: - who had received at least one dose of study vaccine/control according to their random assignment, - for whom the randomization code had not been broken"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details; "Double blind, randomized (2:1) and placebo controlled study with 2 parallel groups"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions
Selective reporting (reporting bias)	Unclear risk	No details
Other bias	Unclear risk	No details

RV1 GSK[033] 2007-LA

Methods	RCT **Length of follow-up:** 1 month after dose 2 **Adverse event data collection methods:** not reported
Participants	**Number:** 228 enrolled; 203 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants, born after a normal gestation period of ≥ 36 weeks; 6 to 12 weeks of age at the time of the first dose of the study vaccination course, free of obvious health problems as established by medical history and clinical examination before entering into the study **Exclusion criteria**: any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the gastrointestinal tract or other serious medical condition as determined by the investigator and previous confirmed occurrence of rotavirus gastroenteritis
Interventions	RV1 1. RIX4414 (RV1): $10^{6.5}$ PFU*; 730 participants (randomized) 1.1. Received RV1 vaccine Lot A 1.2. Received RV1 vaccine Lot B 1.3. Received RV1 vaccine Lot C *Dose unclear, some use $10^{6.5}$ PFU and some 10^{5} PFU 2. Placebo: 124 participants (randomized) **Schedule:** 2 oral doses given at 2 and 4 months; visits 1, 2, and 3 correspond to months 0, 2, and 4 in the schedule
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity: for each type of solicited symptom, occurrence of the symptom within the 8-day (days 0 to 7) solicited follow-up period after each dose; occurrence of unsolicited adverse events within 31 days (days 0 to 30) after each dose, according to MedDRA classification; measured up to 31 days after vaccine/placebo 2. Serious adverse events: occurrence throughout entire study period; measured up to 31 days after vaccine/placebo 3. Drop-outs: measured up to 31 days after vaccine/placebo 4. All-cause death 5. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity** 6. Vaccine virus shedding: presence of rotavirus antigen in stool samples collected on day of vaccination and on planned days following each dose in a subset of participants [review includes data from combined time points] 7. Seroconversion: appearance of serum anti-rotavirus IgA antibody concentrations ≥ 20 U/mL [review includes data from 2 months after dose 2]
Immunization status	Use of other vaccines not mentioned
Location	7 study centres (2 in Colombia, 1 in Mexico, and 4 in Peru) WHO mortality strata B, D
Notes	**Date:** 8 August 2003 to 29 January 2004 **Source of funding:** GlaxoSmithKline Biologicals **Study rationale:** "to assess the clinical consistency of 3 production lots of human ro-

RV1 GSK[033] 2007-LA (*Continued*)

	tavirus vaccine in terms of immunogenicity and safety when given to healthy infants at 2 and 4 months of age"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	No details; "treatment allocation of 2:2:2:1"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions
Selective reporting (reporting bias)	Unclear risk	No details
Other bias	Unclear risk	No details

RV1 GSK[041] 2007-KOR

Methods	RCT **Length of follow-up:** 2 months after dose 2 **Adverse event data collection methods:** not reported
Participants	**Number:** 400 enrolled; 391 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** full-term infants; healthy infants aged between 6 and 12 weeks (42 to 90 days) at the time of the first vaccination for whom the vaccination history was available **Exclusion criteria:** previous confirmed occurrence of rotavirus gastroenteritis
Interventions	RV1 1. RIX4414 (RV1): $10^{6.5}$ PFU; 103 participants (randomized) 2. Placebo: 52 participants (randomized) **Schedule:** 2 oral doses starting at about 2 months of age; second dose at 4 months of age
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity: for each type of solicited symptom, occurrence of the symptom within the 15-day (days 0 to 14) solicited follow-up period after each dose; occurrence of unsolicited adverse events within 43 days (days 0 to 42) after each dose, according to MedDRA classification; up to 43 days after vaccine/placebo

	2. Serious adverse events: no definition; occurrence throughout the entire study period (up to 2 months after dose 2) 3. Drop-outs: measured up to 2 months after dose 2 4. Rotavirus diarrhoea: presence of rotavirus in gastroenteritis episode stools collected from dose 1 of vaccine/placebo up to 2 months after dose 2 5. All-cause death 6. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity** 7. Seroconversion: appearance of anti-rotavirus immunoglobulin A antibody concentration 20 U/mL in participants who were seronegative before vaccination [review includes data from 2 months after dose 2]
Immunization status	*H. influenzae* type b vaccine administered concomitantly along with the 2 doses of vaccine/placebo and at 2 months after dose 2; other routine childhood vaccines were to be given at least 14 days before trial vaccine/placebo
Location	6 centres in Korea WHO mortality stratum B
Notes	**Date:** 15 July 2005 to 11 May 2006 **Source of funding:** GlaxoSmithKline Biologicals **Study rationale:** "to assess immunogenicity and safety of 2 doses of the HRV [human rotavirus] vaccine in Korean infants aged approximately 2 months at the time of the first dose"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The ATP cohort for immunogenicity included all vaccinated subjects: - who had received at least one dose of study vaccine/control according to their random assignment, - for whom the randomization code had not been broken"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details; "Randomized (2:1), double-blind, placebo-controlled study with 2 parallel groups"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions
Selective reporting (reporting bias)	Unclear risk	No details
Other bias	Unclear risk	No details

RV1 GSK[101555] 2008-PHL

Methods	RCT **Length of follow-up:** outcomes measured 1 month after last dose of vaccine/placebo **Adverse event data collection methods:** not reported
Participants	**Number:** 150 enrolled; 145 evaluable **Age range:** 6 to 12 weeks **Inclusion criteria:** healthy, full-term infants aged 6 to 12 weeks; male or female infants between, and including, 6 and 12 weeks of age at the time of the first vaccination, free of obvious health problems, born after a normal gestation period (between 36 and 42 weeks) or with a birth weight > 2000 g **Exclusion criteria:** infants with previous confirmed occurrence of rotavirus gastroenteritis
Interventions	RV1 1. RIX4414 (RV1): $10^{6.5}$; 100 participants* 1.1 Licensed formulation 1.2 Lyophilized formulation 2. Placebo: 50 participants* 2.1 Normal placebo 2.2 Lyophilized formulation **Schedule:** 2 doses given 2 months **Data from the lyophilized formulation, which is not yet approved or marketed, are not reported in review*
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity: for each type of solicited symptom, occurrence of the symptom within the 15-day (day 0 to 14) solicited follow-up period after each dose; occurrence of unsolicited adverse events within 31 (day 0 to 30) days after any doses of RV1 vaccine or placebo, according to MedDRA classification 2. Serious adverse events: occurrence throughout entire study period (up to 31 days after final dose of vaccine/placebo) 3. Drop-outs: measured up to 31 days after final dose of vaccine/placebo 4. Rotavirus diarrhoea: presence of rotavirus in gastroenteritis stools collected until 1 month after dose 2 5. All-cause death 6. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity** 7. Vaccine viral shedding in stool (review includes data from combined time points) 8. Seroconversion: appearance of anti-rotavirus IgA antibody concentration $\geq$ 20 U/mL in participants initially (ie before first dose of vaccine/placebo) negative for rotavirus (review includes data from 2 months after dose 1, 1 month after dose 2, and combined dose 1 and 2 at 1 month after dose 2)
Immunization status	Use of other vaccines not mentioned
Location	1 study centre in the Philippines WHO mortality stratum B

RV1 GSK[101555] 2008-PHL (*Continued*)

Notes	**Date:** 11 May 2004 to 13 September 2004 **Source of funding:** GlaxoSmithKline Biologicals **Trial objective:** "To assess the immunogenicity and safety of 2 different formulations of live attenuated HRV [human rotavirus] vaccine given as a two-dose primary vaccination in healthy infants previously uninfected with HRV"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The ATP cohort for immunogenicity included all vaccinated subjects: - who had received at least one dose of study vaccine/control according to their random assignment, - for whom the randomization code had not been broken"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details; "Double-blind with respect to each HRV [RV1] vaccine formulation and its respective placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions
Selective reporting (reporting bias)	Unclear risk	No details
Other bias	Unclear risk	No details

RV1 Kawamura 2010-JPN

Methods	RCT **Length of follow-up:** up to the age of 2 years **Adverse event data collection methods:** not reported
Participants	**Number:** 765 **Age range:** 6 to 14 weeks **Inclusion criteria:** full-term healthy infants aged 6 to 14 weeks at the time of the first dose **Exclusion criteria:** use of any other investigational or non-registered product (drug or vaccine) within 30 days preceding the first dose of human rotavirus vaccine; history of use of experimental rotavirus vaccine; chronic administration of immunosuppressants or other immune-modifying drugs since birth; concurrently participating in another clinical study; any clinically significant history of a serious medical condition; previous confirmed occurrence of rotavirus gastroenteritis

Interventions	1. RV1, 508 participants 2. Placebo, 257 participants **Schedule:** 2 doses according to a 0, 1 month schedule
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Any rotavirus gastroenteritis leading to medical intervention and caused by the circulating wild-type rotavirus strains, from 2 weeks after dose 2 up to 2 years of age, stool sample collected as soon as possible but preferably not later than 7 days after the start of the episode 2. Severe rotavirus gastroenteritis (≥11 on the Vesikari scale) leading to a medical intervention and caused by the circulating wild-type rotavirus strains (a) of G1 type, (b) of non-G1 types, from 2 weeks after dose 2 up to 2 years of age 3. Each type of solicited symptom (including: cough, diarrhoea, fever, irritability, loss of appetite and vomiting), during the 8-day follow-up period after each dose 4. Adverse events leading to discontinuation of the trial 5. Serious adverse events, including intussusception, up to 2 years of age 6. Fatal serious adverse events 7. Drop-outs before the end of the trial **Outcomes to measure immunogenicity** 8. Seroconversion in terms of anti-rotavirus IgA antibody, from 2 months after dose 2. Seroconversion was defined as the appearance of anti-rotavirus immunoglobulin A antibody concentration over 20 units (U)/millilitre (mL) in subjects initially (ie prior to the first dose of RV1) seronegative
Immunization status	Combined diphtheria and tetanus toxoids and acellular pertussis (DTPa) and Hepatitis B (HBV) vaccines were allowed to be co-administered along with RV1 vaccine/placebo
Location	Japan WHO mortality stratum A
Notes	**Date:** June 2007 - November 2009 **Source of funding:** GlaxoSmithKline **Registration number:** NCT00480324

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomized, no further information given
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)", no further details

RV1 Kawamura 2010-JPN (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition/exclusions balanced between groups
Selective reporting (reporting bias)	Low risk	Protocol published a priori, all pre-published outcomes reported
Other bias	Unclear risk	Study sponsor and collaborator: GlaxoSmithKline

RV1 Kerdpanich 2010-THA

Methods	RCT **Length of follow-up:** 2 months post dose 2 **Adverse event data collection methods:** passive; "Diary cards were provided to the parents/guardians of infants to record the solicited general symptoms occurring during the 15 day follow up period after each vaccine dose. The solicited general symptoms were loss of appetite, fussiness/irritability, fever, diarrhoea, vomiting and cough/runny nose. The intensity of each of these symptoms was graded on a 3-point scale where "0" indicates normal and "3" indicates severe"
Participants	**Number:** 450 enrolled; ATP safety cohort: 447; ATP immunogenicity cohort: 339 **Inclusion criteria:** healthy infants aged 6 to 12 weeks at the time of the first vaccination **Exclusion criteria:** any other investigational drug or vaccine; a history of gastrointestinal disease or rotavirus gastroenteritis; allergy to any of the vaccine components; a history of immunosuppressive or immunodeficient condition
Interventions	1. RIX4414* vaccine reconstituted in buffer stored at 2°C-8°C, n = 174 2. RIX4414* vaccine reconstituted in water stored at 2°C-8°C, n = 174 3. RIX4414* vaccine reconstituted in buffer stored at 37°C for seven days, n = 50 4. Placebo reconstituted in buffer, n = 26 5. Placebo reconstituted in water, n = 26 * Lyophilized formulation containing at least $10^{6.0}$ $CCID_{50}$ of the RIX4414 strain **Schedule:** Two doses at month 0 and 2
Outcomes	**Clinical outcome measures** 1. * Rotavirus diarrhoea, stool sample collected during diarrhoea episode, up to 2 months post dose 2 2. * All-cause diarrhoea, up to 2 months post dose 2 3. Reactogenicity, including fever, vomiting and diarrhoea, 15 day follow-up period after each dose (collected from GSK report) 4. Serious adverse events, up to 2 months post dose 2 5. Fatal serious adverse events 6. Adverse events resulting in discontinuation (collected from GSK report) 7. Drop-outs: measured up to 2 months after dose 2 (collected from GSK report) **Outcomes to measure immunogenicity** 8. Seroconversion, anti-rotavirus IgA antibody levels (cut off: $\geq$ 20 U/mL by ELISA), two months post dose 2 9. Rotavirus antigen shedding in stool [review includes data from combined time points]

	(collected from GSK report) * Outcome reported as proportion (P) with 95% CI. Events (n) and totals (N) were estimated by using the values when two formulas for the standard error (SE) converged
Immunization status	"During the study period, participating infants were offered commercially available GSK Biologicals' diphtheria toxoid, tetanus toxoid, acellular pertussis, inactivated polio and *H. influenzae* type b combination vaccine (*Infanrix*^{TM} -IPV/Hib) at two and four months of age and diphtheria toxoid, tetanus toxoid, acellular pertussis, hepatitis B, inactivated polio and *H. influenzae* type b combination vaccine (*Infanrix hexa*^{TM}) at six months of age"
Location	Two centres in Thailand WHO mortality stratum B
Notes	Study known as *RIX GSK[039] 2007-AS* in previously published versions of this review. **Date:** March to December 2005 **Source of funding:** GSK Biologicals **Study rationale:** This study evaluated the stability of lyophilized RIX4414 vaccine in terms of immunogenicity when reconstituted in water instead of regular buffer, and when stored at tropical room temperature (37 °C) for 7 days before reconstitution

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomized", no further details reported
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding (performance bias and detection bias) All outcomes	High risk	Partially blind study "Single blind", not reported whether personnel or participants were blinded "The placebo was identical in appearance and composition to the active vaccine"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition balanced across groups with reasons for withdrawal reported
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	Unclear risk	Funded by GSK Biologicals

RV1 Madhi 2010-AF

Methods	RCT **Length of follow-up:** outcomes measured 2 weeks after last dose to 1 year of age, and at two years **Adverse event data collection methods:** active surveillance for all gastroenteritis episodes was conducted by members of the study staff through weekly visits to parents or guardians to collect diary cards and through the collection of data from health clinics that served the study populations
Participants	**Number:** 4939 enrolled; 4417 evaluable **Age range:** 1 to 6 months **Inclusion criteria:** healthy infants aged 6 to 10 weeks for the group receiving 3 doses and 10 to 14 weeks for the group receiving 2 doses of RV1 **Exclusion criteria:** children HIV positive that were immunosuppressed at < 6 weeks before vaccination
Interventions	RV1 1. RIX4414 (RV1): dose same as commercial; 3298 participants 1.1 2 doses 1.2 3 doses 2. Placebo: 1641 participants 2.1 Normal placebo **Schedule:** 2 to 3 doses given 1 month apart
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. All-cause diarrhoea 2. Rotavirus diarrhoea: stool samples were tested for rotavirus with the use of an enzyme-linked immunosorbent assay (ELISA) (Rotaclone, Meridian Bioscience) 3. Severe rotavirus diarrhoea: the severity of each episode of gastroenteritis was evaluated with the use of the Vesikari scale 13 (on which scores range from 1 to 20, with higher scores indicating greater severity) and was categorized as severe if the score was 11 or more * 4. Severe all-cause diarrhoea: the severity of each episode of gastroenteritis was evaluated with the use of the Vesikari scale 13 (on which scores range from 1 to 20, with higher scores indicating greater severity) and was categorized as severe if the score was 11 or more 5. All-cause mortality: all serious adverse events including deaths were recorded for the period between the date the first dose of vaccine or placebo was administered and the date the child reached 1 year of age 6. Serious adverse events: all serious adverse events including deaths were recorded for the period between the date the first dose of vaccine or placebo was administered and the date the child reached 1 year of age **Outcomes to measure immunogenicity** 7. Immunogenicity: ELISA - 1 month after the last dose to determine the serum concentrations of antirotavirus IgA antibody
Immunization status	Vaccines that are administered routinely according to the guidelines of the Expanded Program on Immunization (EPI) were concomitantly administered with the vaccine or placebo, including oral polio vaccine

RV1 Madhi 2010-AF (*Continued*)

Location	South Africa and Malawi WHO mortality stratum E
Notes	This trial was conducted in Malawi and South Africa, data reported separately per country can be found under RV1 Madhi 2010-MWI and RV1 Madhi 2010-ZAF **Date:** October 2005 to February 2007 (South Africa); October 2006 to July 2007 (Malawi) **Source of funding:** PATH Rotavirus Vaccine Program and GlaxoSmithKline

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A randomizations list was generated at GSK Biologicals, Rixensart, using a standard SAS® (Statistical Analysis System) program and this was used to number the vaccines
Allocation concealment (selection bias)	Low risk	The vaccine doses were distributed to each study centre while respecting the randomizations block size
Blinding (performance bias and detection bias) All outcomes	Low risk	The site investigator, who was unaware of the group assignments of the children
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Unclear risk	Sponsored by industry

RV1 Madhi 2010-MWI

Methods	RCT **Length of follow-up:** outcomes measured 2 weeks after last dose to 1 year of age, and at two years **Adverse event data collection methods:** active surveillance for all gastroenteritis episodes was conducted by members of the study staff through weekly visits to parents or guardians to collect diary cards and through the collection of data from health clinics that served the study populations
Participants	**Number:** 1773 enrolled **Age range:** 1 to 6 months **Inclusion criteria:** healthy infants aged 6 to 10 weeks for the group receiving 3 doses and 10 to 14 weeks for the group receiving 2 doses of RV1

RV1 Madhi 2010-MWI (*Continued*)

	Exclusion criteria: children HIV positive that were immunosuppressed at < 6 weeks before vaccination
Interventions	RV1 1. RIX4414 (RV1): dose same as commercial; 1182 participants 1.1 2 doses 1.2 3 doses 2. Placebo: 591 participants 2.1 Normal placebo **Schedule:** 2 to 3 doses given 1 month apart
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. All-cause diarrhoea 2. Rotavirus diarrhoea: stool samples were tested for rotavirus with the use of an ELISA (Rotaclone, Meridian Bioscience) 3. Severe rotavirus diarrhoea: the severity of each episode of gastroenteritis was evaluated with the use of the Vesikari scale 13 (on which scores range from 1 to 20, with higher scores indicating greater severity) and was categorized as severe if the score was 11 or more* 4. Severe all-cause diarrhoea: the severity of each episode of gastroenteritis was evaluated with the use of the Vesikari scale 13 (on which scores range from 1 to 20, with higher scores indicating greater severity) and was categorized as severe if the score was 11 or more 5. All-cause mortality: all serious adverse events including deaths were recorded for the period between the date the first dose of vaccine or placebo was administered and the date the child reached 1 year of age 6. Serious adverse events: all serious adverse events including deaths were recorded for the period between the date the first dose of vaccine or placebo was administered and the date the child reached 1 year of age **Outcomes to measure immunogenicity** 7. Immunogenicity: ELISA - 1 month after the last dose to determine the serum concentrations of antirotavirus IgA antibody
Immunization status	Vaccines that are administered routinely according to the guidelines of the Expanded Program on Immunization (EPI) were concomitantly administered with the vaccine or placebo, including oral polio vaccine
Location	Malawi WHO mortality stratum E
Notes	This trial was conducted in Malawi and South Africa, this part presents data reported for the Malawi cohort, data reported for South Africa can be found under RV1 Madhi 2010-ZAF, data reported for both countries under RV1 Madhi 2010-AF **Date:** October 2006 to July 2007 **Source of funding:** PATH Rotavirus Vaccine Program and GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement

RV1 Madhi 2010-MWI (*Continued*)

Random sequence generation (selection bias)	Low risk	A randomizations list was generated at GSK Biologicals, Rixensart, using a standard SAS® (Statistical Analysis System) program and this was used to number the vaccines
Allocation concealment (selection bias)	Low risk	The vaccine doses were distributed to each study centre while respecting the randomizations block size
Blinding (performance bias and detection bias) All outcomes	Low risk	The site investigator, who was unaware of the group assignments of the children
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Unclear risk	Sponsored by industry

RV1 Madhi 2010-ZAF

Methods	RCT **Length of follow-up:** outcomes measured 2 weeks after last dose to 1 year of age, and at two years (only Cohort 2) **Adverse event data collection methods:** active surveillance for all gastroenteritis episodes was conducted by members of the study staff through weekly visits to parents or guardians to collect diary cards and through the collection of data from health clinics that served the study populations
Participants	**Number:** 3166 enrolled **Age range:** 1 to 6 months **Inclusion criteria:** healthy infants aged 6 to 10 weeks for the group receiving 3 doses and 10 to 14 weeks for the group receiving 2 doses of RV1 **Exclusion criteria:** children HIV positive that were immunosuppressed at < 6 weeks before vaccination
Interventions	RV1 1. RIX4414 (RV1): dose same as commercial; 2116 participants 1.1 2 doses 1.2 3 doses 2. Placebo: 1050 participants 2.1 Normal placebo **Schedule:** 2 to 3 doses given 1 month apart
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. All-cause diarrhoea

	2. Rotavirus diarrhoea: stool samples were tested for rotavirus with the use of an ELISA (Rotaclone, Meridian Bioscience) 3. Severe rotavirus diarrhoea: the severity of each episode of gastroenteritis was evaluated with the use of the Vesikari scale 13 (on which scores range from 1 to 20, with higher scores indicating greater severity) and was categorized as severe if the score was 11 or more* 4. Severe all-cause diarrhoea: the severity of each episode of gastroenteritis was evaluated with the use of the Vesikari scale 13 (on which scores range from 1 to 20, with higher scores indicating greater severity) and was categorized as severe if the score was 11 or more 5. All-cause mortality: all serious adverse events including deaths were recorded for the period between the date the first dose of vaccine or placebo was administered and the date the child reached 1 year of age 6. Serious adverse events: all serious adverse events including deaths were recorded for the period between the date the first dose of vaccine or placebo was administered and the date the child reached 1 year of age **Outcomes to measure immunogenicity** 7. Immunogenicity: ELISA - 1 month after the last dose to determine the serum concentrations of antirotavirus IgA antibody *G types for severe rotavirus diarrhoea for the first year follow-up was reported and added to the analyses, G types for any rotavirus diarrhoea was reported for the second year only, and was not added to the analysis
Immunization status	Vaccines that are administered routinely according to the guidelines of the Expanded Program on Immunization (EPI) were concomitantly administered with the vaccine or placebo, including oral polio vaccine
Location	South Africa WHO mortality stratum E
Notes	This trial was conducted in Malawi and South Africa, this part presents data reported for the South Africa cohorts, data reported for Malawi can be found under RV1 Madhi 2010-MWI, data reported for both countries under RV1 Madhi 2010-AF **Date:** October 2005 to February 2007 **Source of funding:** PATH Rotavirus Vaccine Program and GlaxoSmithKline

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A randomizations list was generated at GSK Biologicals, Rixensart, using a standard SAS® (Statistical Analysis System) program and this was used to number the vaccines
Allocation concealment (selection bias)	Low risk	The vaccine doses were distributed to each study centre while respecting the randomizations block size

RV1 Madhi 2010-ZAF (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	The site investigator, who was unaware of the group assignments of the children
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Unclear risk	Sponsored by industry

RV1 Narang 2009-IND

Methods	RCT **Length of follow-up:** 1 month after dose 2 **Adverse event data collection methods:** passive, parents/guardians filled in diary cards of any symptoms
Participants	**Number:** 363 enrolled; 344 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy male or female infant between and including, 8 to 10 weeks of age at the time of first vaccination; free of obvious health problems as established by medical history and clinical examination before entering into the study; subjects had been administered the first dose of diphtheria, tetanus, pertussis, hepatitis B, *H. influenzae* type b, oral poliovirus vaccine as per the local universal immunization programme at age 6 weeks (given with a 2-week separation from the first and subsequent dose of the RV1 vaccine or placebo) **Exclusion criteria**: history of confirmed rotavirus gastroenteritis or with prior administration of experimental rotavirus vaccine
Interventions	RV1 1. RIX4414 (RV1): $10^{6.5}$ PFU; 182 participants (randomized) 2. Placebo: 181 participants (randomized) **Schedule:** 2 oral doses given at age 2 and 4 months
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity: for each type of solicited symptom, occurrence of the symptom within the 8-day (days 0 to 7) solicited follow-up period after each dose; occurrence of unsolicited adverse events within 31 days (days 0 to 30) after each dose, according to MedDRA classification; measured up to 31 days after vaccine/placebo 2. Serious adverse events: no definition; occurrence throughout entire study period (up to 31 days after vaccine/placebo) 3. Drop-outs: no definition; measured up to 31 days after vaccine/placebo 4. Rotavirus diarrhoea: presence of rotavirus in gastroenteritis episode stools collected from dose 1 of RV1 vaccine/placebo up to 2 months after dose 2; measured up to 31 days after vaccine/placebo 5. All-cause death 6. Adverse events resulting in discontinuation

RV1 Narang 2009-IND (*Continued*)

	Outcomes to measure immunogenicity 7. Seroconversion: appearance of anti-rotavirus immunoglobulin A (IgA) antibody concentration $\geq$ 20 U/mL in participants who were seronegative before vaccination [review includes data from 1 month after dose 2]
Immunization status	Routine vaccinations (diphtheria-tetanus-whole cell pertussis-hepatitis b, *H. influenzae* type b, and oral poliovirus vaccine) were administered at 6, 10, and 14 weeks of age (given with a 2-week separation from the first and subsequent dose of the RV1 vaccine or placebo)
Location	4 centres in India WHO mortality stratum D
Notes	**Date:** 10 February 2006 to 8 September 2006 **Source of funding:** GlaxoSmithKline Biologicals **Study rationale:** "to assess the immunogenicity and safety of 2 doses of oral live attenuated human rotavirus vaccine in healthy infants in India"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The ATP cohort for immunogenicity included all vaccinated subjects: - who had received at least one dose of study vaccine/control according to their random assignment, - for whom the randomization code had not been broken", no further details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double-blind", no further details
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition/exclusions balanced between groups
Selective reporting (reporting bias)	Unclear risk	Not enough details were provided
Other bias	Unclear risk	Funded by industry

RV1 Omenaca 2012-EU

Methods	RCT **Length of follow-up:** 30 to 83 days after dose two **Adverse events data collection methods:** active surveillance: at each study visit parens were asked about AEs; passive surveillance: throughout the trial, parents were asked to immediately report AEs to the investigator
Participants	**Number:** 1009 **Age range:** 6 to 12 weeks of age at the time of the first study vaccination **Inclusion criteria:** medically stable pre-term infants, born within a gestational period of 27-36 weeks, planned to be discharged from hospital's neonatal stay on or before the day of the first human rotavirus vaccine/placebo administration **Exclusion criteria:** use of any investigational or non-registered product (drug or vaccine) other than the human rotavirus vaccine within 30 days preceding the first dose of human rotavirus vaccine; any clinically significant history of chronic gastrointestinal disease; any confirmed or suspected immunosuppressive or immunodeficient condition; history of allergic disease; major congenital defects or serious chronic illness **Notes:** each study group is further stratified into two subgroups depending on the gestational age at birth of the subject: Stratum I: very pre-term infants, born after a gestational period of 27 to 30 weeks (189 to 216 days) (20% of enrolment); Stratum II: mild pre-term infants born after a gestational period of 31 to 36 weeks (217 to 258 days) (80% of enrolment)
Interventions	1. RV1, 670 participants 2. Placebo, 339 participants **Schedule:** 2 oral doses of vaccine or placebo, 1 dose at Day 0 and 1 dose at month 1 or 2, depending on the country
Outcomes	**Clinical outcome measures** 1. Serious adverse events, including fatal events and intussusception, from Day 0 up to 83 days after dose 2 of RV1 vaccine/placebo 2. Solicited symptoms, within 15 days after each RV1 vaccine/placebo dose. Solicited symptoms included diarrhoea (3 or more looser than normal stools/day), fever (axillary temperature over 37.5 °C), irritability, loss of appetite, and vomiting 3. All-cause gastroenteritis and rotavirus gastroenteritis, from Dose 1 up to 83 days after Dose 2 of RV1 vaccine/placebo. Gastroenteritis: diarrhoea with or without vomiting. Rotavirus gastroenteritis: a gastroenteritis episode was a rotavirus gastroenteritis episode if a stool sample taken during or not later than 7 days after the episode was rotavirus positive by ELISA 4. Drop-outs before the end of the trial **Outcomes to measure immunogenicity** 5. Seroconversion to anti-rotavirus IgA antibody, at Visit 3, 1 month after Dose 2 of RV1 vaccine/placebo. Number of subjects with anti-rotavirus IgA antibody concentration over 20 Units/mL
Immunization status	In accordance with the local National Plan of Immunisation schedule in each of the respective participating countries, GSK Biologicals' Infanrix Hexa® (DTPa-HBV-IPV/Hib), Infanrix Quinta® (DTPa-IPV-Hib), Infanrix®+IPV+Hib (DTPa+IPV+Hib) and/or Engerix-B® (HBV) will be co-administered (at a maximum interval of two days from each other) with each human rotavirus vaccine or placebo dose Hepatitis B and Bacille Calmette-Guérin vaccines (BCG) at birth are allowed if included

	in the local National Plan of Immunisation schedule in participating countries At the discretion of the investigator the following vaccines may be administered during each subject's study participation: • Vaccine against *S. pneumoniae* (Prevenar®) in France and Spain (concomitantly with human rotavirus vaccine/placebo). • Vaccine against *Neisseria meningitidis* (Neis Vacc C®) is allowed if there is at least 14-days interval with respect to the administration of the human rotavirus vaccine/ placebo.
Location	France, Poland, Portugal, Spain WHO mortality strata A, B
Notes	Study known as *RV1 NCT00420745 2009-EU* in previously published versions of this review. **Date:** January 2007 to March 2008 **Source of funding:** GlaxoSmithKline **Registration number:** NCT00420745

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated block randomizations
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)", no further information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced between groups
Selective reporting (reporting bias)	Low risk	All expected outcomes included
Other bias	Unclear risk	Sponsor: GlaxoSmithKline

RV1 Phua 2005-SGP

Methods	RCT **Length of follow-up:** until infants aged 18 months (ie about 13 to 15 months of follow-up) **Adverse events data collection methods:** "diary cards during a 15-day follow-up period after each vaccine dose was administered, and the symptoms were graded according to severity. AEs occurring up to 42 days after administration of each study vaccine was recorded" (passive method)
Participants	**Number:** 2464 enrolled; 2365 evaluable **Age range:** 3 to 6 months **Inclusion criteria:** male or female infants, born after a normal gestation period of 36 to 42 weeks; aged 11 to 17 weeks at time of first dose of study vaccine; free of obvious health problems as established by medical history and clinical examination before entering into the study **Exclusion criteria:** "Subjects with previous confirmed occurrence of rotavirus gastroenteritis, previous vaccination against or history of diphtheria, tetanus, pertussis, polio and/or Hib, had a history of allergic reaction to any vaccine component, were immunocompromised or had contact with immunosuppressed individual or pregnant women in their household, had any clinically significant history of chronic gastrointestinal (GI) disease including any uncorrected congenital malformation of GI tract or subjects with use of antibiotics within 7 days preceding Dose 1"
Interventions	RV1 1. RIX4414 (RV1) 1.1. $10^{4.7}$ focus forming units (FFU); 510 participants 1.2. $10^{5.2}$ FFU; 648 participants 1.3. $10^{6.1}$ FFU; 653 participants 2. Placebo; 653 participants All vaccines given in 2 doses with a 1-month interval *Outcomes measured at 15 months (efficacy data from 2 weeks after second dose to 18 months of age)*
Outcomes	**Clinical outcome measures** 1. All-cause diarrhoea: episodes of acute gastroenteritis; parents instructed to record (diary cards) body temperature, the number of episodes of vomiting, the number of looser-than-normal stools, and whether they sought medical intervention or medication, and were asked to obtain at least 2 stool samples on 2 different days within 7 days of the onset of symptoms; measured at 2 weeks to 18 months 2. Rotavirus diarrhoea: see all-cause diarrhoea; "Rotavirus gastroenteritis was confirmed if at least 1 of the 2 stool specimens was found to be positive for rotavirus by ELISA. Rotavirus isolates were G-typed by use of reverse-transcriptase polymerase chain reaction (RT-PCR)"; measured at 2 weeks to 18 months 3. Severe all-cause diarrhoea: severity of each episode of gastroenteritis graded using a 20-point scoring system described by Ruuska 1990 4. Severe rotavirus diarrhoea: see severe all-cause diarrhoea 5. All-cause death 6. All-cause hospital admission 7. Emergency department visit 8. Serious adverse events

	9. Reactogenicity: fever if rectal temperature > 38 ºC 10. Adverse events requiring discontinuation 11. Rotavirus diarrhoea requiring hospitalization 12. Drop-outs **Outcomes to measure immunogenicity** 11. Shedding of vaccine virus: in stool samples on day of each vaccination and on days 7 and 15 after each vaccination (from 50 participants/group, the "stool sample subset") [review includes data from 1 month after dose 1 and 1 month after dose 2] 12. Seroconversion: serum anti-rotavirus IgA antibody seroconversion rate; "seroconversion" "defined by an anti-rotavirus IgA antibody concentration of ≥ 20 U/mL, for infants who were initially (i.e. before administration of the first vaccine dose) seronegative for anti-rotavirus IgA antibodies (i.e. a concentration of <20 U/mL) and/or who had a stool sample that was negative for rotavirus antigen. Any detection of RIX4414 antigen in stool samples was taken as evidence of a vaccine response"
Immunization status	Hepatitis B vaccine, diphtheria-tetanus-acellular pertussis, poliovirus, and *H. influenzae* type b co-administered with interventions
Location	8 centres in Singapore WHO mortality stratum A
Notes	**Date:** 4 January 2001 to 15 April 2003 **Funding:** GlaxoSmithKline Biologicals **Other:** 93% of population were Asian

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details: "Infants were randomly assigned (on a 1:1:1 basis)"; "randomized, double-blind, placebo-controlled study"
Allocation concealment (selection bias)	Unclear risk	No details: "randomized, double-blind, placebo-controlled study"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details: "double-blind, placebo-controlled study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data imputed appropriately
Selective reporting (reporting bias)	Unclear risk	Reasons for low number of rotavirus gastroenteritis; "A smaller number of rotavirus-related gastroenteritis cases than expected were documented during the study. For 41% (160/387) of the reported gastroenteritis episodes, stool samples were not

RV1 Phua 2005-SGP (*Continued*)

		available for determination of the etiology of the gastroenteritis. No results were available for 6% (24/387) of the gastroenteritis episodes because of an insufficient quantity of stool samples collected or because of invalid results"
Other bias	Unclear risk	See above

RV1 Phua 2009-AS

Methods	RCT **Length of follow-up:** 2 weeks post dose 2 to 3 years **Adverse events data collection methods:** passive method, using diary cards
Participants	**Number:** 10,708 enrolled; 10,519 evaluable **Age range:** 3 to 6 months **Inclusion criteria:** healthy infants 6 to 12 weeks of age in Hong Kong and Taiwan, or 11 to 17 weeks of age in Singapore at the time of the first dose **Exclusion criteria:** "they did not have a history of chronic administration of immunosuppressants since birth, any confirmed or suspected immunosuppressive or immunodeficient condition, history of allergic disease or reaction likely to be exacerbated by any vaccine component, had not received any investigational drugs/vaccines from 30 days before Dose 1 or planned use during the study, had not received immunoglobulins and/or blood products since birth or planned administration during the study period, did not have any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the gastrointestinal tract or other serious medical condition as determined by the investigator, and did not have first or second degree of consanguinity of parents"
Interventions	RV1 1. RIX4414 (RV1) 10^6 FFU; 5359 participants 2. Placebo; 5349 participants All vaccines given in 2 doses with a 1 to 2 month interval
Outcomes	**Clinical outcome measures** 1. All-cause diarrhoea: a gastroenteritis episode was defined as occurrence of diarrhoea with or without vomiting (diarrhoea was defined as the passage of three or more looser than normal stool within a 24 h period) 2. Severe all-cause diarrhoea: severe gastroenteritis was defined as an episode of diarrhoea with or without vomiting that required overnight hospitalization and/or rehydration therapy (equivalent to WHO plan B or C) in a medical facility and with a score 11 points on the 20-point Vesikari scale 3. Rotavirus diarrhoea: stool samples collected during gastroenteritis episodes were tested for the presence of rotavirus using ELISA method (Rotaclone^{TM}, Meridian Bioscience) at GlaxoSmithKline Biologicals' laboratories in Rixensart, Belgium. All rotavirus-positive stool samples were tested by reverse transcriptase polymerase chain reaction (RT-PCR) followed by reverse hybridization assay, and optional sequencing, at Delft Diagnostic Laboratory, The Netherlands to determine G and P types, and differentiation of G1P[8]

	vaccine type 4. Severe rotavirus diarrhoea*: see above 5. Emergency department visit: active surveillance was conducted at hospitals and medical facilities in the study area to capture gastroenteritis episodes requiring hospitalization and/or re-hydration therapy (equivalent to WHO plan B or C) in a medical facility from day of the first vaccine or placebo dose until the follow-up visit at 24 months of age 6. Serious adverse events: intussusception and serious adverse events (SAEs) were followed during the study duration. A case of definite intussusception required confirmation at surgery or autopsy or by using imaging techniques such as gas or liquid contrast enema or abdominal ultrasound. Abstractable data for all serious adverse events and Kawasaki disease were only provided for the third year of follow-up Intussusception data for the third year follow-up was not included in the analysis as the follow-up population was smaller (RV1: 2/4272; Placebo: 1/4226) 7. All-cause deaths **Outcomes to measure immunogenicity** None *G types for severe rotavirus diarrhoea up to two years follow-up was reported and added to the analyses, data for the third year was reported but not included in the analysis as the follow-up population was smaller
Immunization status	Infants received other routine paediatric immunisations (combined diphtheria toxoid-tetanus toxoid-acellular pertussis [DTPa] inactivated poliovirus [IPV] and *H. influenzae* type b [HiB] vaccine and hepatitis B vaccine [HBV]) during the study period according to local schedules. Almost all infants received BCG dose at birth. If oral polio vaccine (OPV) was given as part of the routine schedule in the participating countries, a time interval of 2 weeks was observed between the OPV doses and RIX4414 vaccine/placebo doses. One dose of oral polio vaccine (OPV) was given at birth in Hong Kong (99. 8% subjects) and Taiwan (0.7% subjects). However, during the study period, >95% of infants in the three countries received DTPa-IPV-HiB concomitantly with both doses of RIX4414 vaccine/placebo as per local schedules 50.9% of subjects were male and the study population was predominantly Chinese (76.3%)
Location	Hong Kong, Singapore, Taiwan WHO mortality stratum A
Notes	**Date:** 8 December 2003 to 31 August 2005 **Funding:** GlaxoSmithKline **Other:** all enrolled infants received the first dose of RIX4414 vaccine or placebo, and 10,551 (98.5%) received both doses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A randomization list was generated at GSK Biologicals, Rixensart, using a standard SAS® program and was used to number the vaccines

RV1 Phua 2009-AS (*Continued*)

Allocation concealment (selection bias)	Low risk	A randomization blocking scheme was used to ensure that the balance between treatments was maintained. Treatment allocation at the investigator sites was performed using a central randomization system on the Internet
Blinding (performance bias and detection bias) All outcomes	Low risk	Data analysis was performed at GSK Biologicals. The treatment code remains masked, except for statisticians and the database administrator
Incomplete outcome data (attrition bias) All outcomes	Low risk	Primary analysis of efficacy was performed from 2 weeks post dose 2 until 2 years of age on the "according-to-protocol" (ATP) cohort that included participants who completed the full two-dose vaccination course and complied with the protocol. The total vaccinated cohort was used to calculate vaccine efficacy starting from the first dose onwards
Selective reporting (reporting bias)	Low risk	All expected outcomes included
Other bias	Unclear risk	Study sponsored by GlaxoSmithKline Biologicals

RV1 Rivera 2011-DOM

Methods	RCT **Length of follow-up:** 17 weeks **Adverse events data collection methods:** not reported
Participants	**Number:** 200 **Age range:** 6 to 14 weeks of age at the time of the first study vaccination **Inclusion criteria:** healthy infants with a live twin living in the same household who is also enrolled in this study, born after a gestation period of over 32 weeks **Exclusion criteria:** use of any investigational or non-registered product other than the study vaccine(s); any confirmed or suspected immunosuppressive or immunodeficient condition; any clinically significant history of chronic gastrointestinal disease; history of allergic disease; acute disease at time of enrolment; gastroenteritis within 7 days preceding the first study vaccine administration; documented HIV-positive subject
Interventions	1. RV1 (RIX 4414) Vaccine, 100 participants 2. Placebo, 100 participants **Schedule:** both vaccine and placebo 2 doses at Day 0 (Visit 1) and Week 7 (Visit 2) **Notes:** one complimentary dose of RV1 was administered to all infants enrolled in this study (both study groups) who are aged less than 6 months at Visit 3 (Week 13) as a

	benefit to the placebo group for participation in the study
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Gastroenteritis, up to week 17 2. Rotavirus gastroenteritis, up to week 13. Rotavirus gastroenteritis episodes were defined as gastroenteritis episodes for which the stool sample temporally closest to the onset day of the gastroenteritis episode was positive for rotavirus by ELISA 3. Serious adverse events, including fatal serious adverse events and intussusception, up to week 17 4. Drop-outs from the study **Outcomes to measure immunogenicity** 5. Anti-rotavirus IgA antibody seroconversion and concentration in each group, at visit 3
Immunization status	All infants received three doses of combined diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliovirus and *H. influenzae* vaccine
Location	Dominican Republic WHO mortality stratum B
Notes	Study known as *RV1 NCT00396630 2009-LA* in previously published versions of this review. **Date:** January 2007 to February 2008 **Source of funding:** GlaxoSmithKline **Registration number:** NCT00396630 **Aim:** "to explore horizontal transmission of the HRV [human rotavirus] vaccine strain within a family from the twin vaccinated with Rotarix to the twin receiving placebo"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A randomization list was generated at GlaxoSmithKline (GSK) Biologicals, Rixensart, using a standard SAS® program. A randomization blocking scheme (1:1 ratio, block size = 2) was used to ensure balance between the treatment arms; a treatment number uniquely identified the vaccine doses to be administered to the same infant"
Allocation concealment (selection bias)	Low risk	"No investigator or any person involved in the clinical trial (including laboratory personnel, statisticians and data management) was aware of the treatment groups during the course of the study"

RV1 Rivera 2011-DOM (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	"The study was double-blinded and the parents/guardians of infants, investigator and the study personnel were unaware of the study vaccine administered"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition/exclusions balanced between groups
Selective reporting (reporting bias)	Low risk	Trial report does not provide enough details
Other bias	Unclear risk	Study sponsor: GlaxoSmithKline

RV1 Ruiz-Palac 06-LA/EU

Methods	RCT **Length of follow-up:** 9 to 10 months **Adverse events data collection methods:** active surveillance system established at hospital and medical facilities in study areas to capture intussusceptions and severe gastroenteritis episodes (active method)
Participants	**Number:** 63,225 enrolled for safety and 20,169 enrolled for efficacy; 59,308 evaluable for safety, and 17,882 evaluable for first year efficacy and 14,615 for second year efficacy **Age range:** 1 to 3 months (start) and 3 to 6 months (end) **Inclusion criteria:** healthy infants aged 6 to 12 weeks (in all countries except Chile) or 6 to 13 weeks (in Chile) at time of first dose of RV1 or placebo; "healthy infants 6-13 weeks of age at the time of the first study vaccination whose parent/guardian sign a written informed consent and whose parents/guardians can and will comply with the requirements of the protocol (eg, completion of the diary cards, return for follow-up visits)" **Exclusion criteria (from NCT00140673):** use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days preceding the first dose of study vaccine or placebo, or planned use during the study period; chronic administration (defined as > 14 days) of immunosuppressants or other immune-modifying drugs since birth (topical steroids allowed); child unlikely to remain in the study area for the duration of the study; any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection; history of allergic disease or reaction likely to be exacerbated by any component of the vaccine; administration of immunoglobulins and/or blood products since birth or planned administration during the study period; any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the gastrointestinal tract or other serious medical condition as determined by the investigator
Interventions	RV1 1. RIX4414 (RV1): $10^{6.5}$ PFU; 31,673 participants (safety), 10,159 participants (efficacy) 2. Placebo; 31,552 participants (safety), 10,010 participants (efficacy) Both vaccine and placebo given in 2 doses with 4 to 8 weeks interval

	Both vaccine and placebo reconstituted in 1.3 mL of liquid calcium carbonate buffer
Outcomes	**Clinical outcome measures** 1. Serious adverse events: "defined as any new health-related problems that resulted in death, were life-threatening, necessitated hospitalization or prolongation of existing hospitalization, or resulted in disability or incapacity"; "case of definite intussusception required confirmation at surgery or autopsy or with the use of imaging techniques, such as imaging with gas- or liquid-contrast enema or abdominal ultrasonography"; measured up to 30 days after vaccination and during the first year follow-up for efficacy; intussusception measured up to 100 days after dose 1. Final intussusception results taken from CDC report (CDC 2010) 2. Severe all-cause diarrhoea: severe gastroenteritis measured as an "episode of diarrhoea with or without vomiting that required hospitalization and/or re-hydration therapy (equivalent to WHealth O plan B or C) in a medical facility"; measured from 2 weeks after second dose up to 2 years follow-up 3. All-cause diarrhoea; measured from 2 weeks after second dose up to 2 years follow-up 4. Rotavirus diarrhoea; measured from 2 weeks after second dose up to 2 years follow-up 5. Severe rotavirus diarrhoea: severe rotavirus gastroenteritis defined as an "an episode of severe gastroenteritis occurring at least 2 weeks after the full vaccination course in which rotavirus other than vaccine strain was identified in a stool sample collected during the episode of severe gastroenteritis"; measured from 2 weeks after second dose up to 2 years follow-up 6. All-cause death; measured up to 30 days after vaccination 7. All-cause hospital admission; from 2 weeks after second dose up to 2 years follow-up 8. Reactogenicity; up to 30 days after vaccination 9. Drop-outs; measured up to 2 years follow-up 11. Rotavirus diarrhoea requiring hospitalizations 12. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity** 13. Seroconversion: serum rotavirus IgA antibody concentrations in a subset of 100 participants per country (except in Finland) at Visits 1 and 3 [data not included in review because it was not a random sample] *Outcomes measured up to 30 days after second dose of vaccine (safety outcomes) and up to 2 years (efficacy outcomes)*
Immunization status	Routine immunizations according to local regulations; oral poliovirus vaccination at least 2 weeks before or after rotavirus vaccine
Location	Latin America and Europe (Argentina, Brazil, Chile, Colombia, Dominican Republic, Finland, Honduras, Mexico, Nicaragua, Panama, Peru, and Venezuela); second year follow-up in all locations except Finland and Peru WHO mortality strata A, B, D
Notes	**Date:** 5 August 2003 to 20 October 2005 **Source of funding:** GlaxoSmithKline Biologicals Data extracted from appendix accompanying main report and GlaxoSmithKline companion reports

RV1 Ruiz-Palac 06-LA/EU (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"GlaxoSmithKline Biologicals provided vaccine supplies that were numbered with a computer-generated randomization list. We used a blocking scheme randomization. GSK did the masking and concealment"
Allocation concealment (selection bias)	Low risk	"Randomization was done by a central Internet randomization system"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Treatment allocation remained concealed from investigators and parents of participating infants throughout the study. GSK did the masking and concealment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"full GSK report account for all withdrawals regardless of reason"
Selective reporting (reporting bias)	High risk	The trial reported only on severe episodes of rotavirus diarrhoea and all-cause diarrhoea, and not on diarrhoea of any severity, which is unusual in these trials
Other bias	Unclear risk	Study sponsored by GlaxoSmithKline Biologicals

RV1 Salinas 2005-LA

Methods	RCT **Length of follow-up:** up to 2 years (stated in GlaxoSmithKline report) **Adverse event data collection methods:** diary cards were supplied to the parents to record occurrence of specific solicited symptoms for 15 days after each vaccination (passive method); any other unsolicited symptoms were recorded during 43 days after each vaccination (passive method); serious adverse events were recorded throughout the study
Participants	**Number:** 2155 enrolled; 2004 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants, born after a normal gestation period of 36 to 42 weeks or with a birth weight > 2000 g; aged 6 to 12 weeks at the time of the first vaccination; free of obvious health problems as established by medical history and clinical examination before entering into the study **Exclusion criteria:** previous confirmed occurrence of rotavirus gastroenteritis; previous vaccination against or history of diphtheria, tetanus, pertussis, polio and/or *H. influenzae* type b vaccine (HiB); any clinically significant history of chronic gastrointestinal disease

	including any uncorrected congenital malformation of gastrointestinal tract; use of antibiotics within 7 days preceding dose 1; immunocompromised or were in household contact with an immunosuppressed individual or pregnant woman
Interventions	RV1 1. RIX4414 (RV1) 1.1. $10^{4.7}$ PFU; 538 participants (randomized) 1.2. $10^{5.2}$ PFU; 540 participants (randomized) 1.3. $10^{5.8}$ PFU; 540 participants (randomized) 2. Placebo: 537 participants (randomized) **Schedule:** 2 doses given every 2 months *An additional 200 participants were* randomized *to RV1 x placebo to receive 3 doses. This is not mentioned on the main publication, only in the GlaxoSmithKline report (no data available)*
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Serious adverse events: no definition; measured during follow-up (2 years) 2. Reactogenicity: no definition; measured up to 43 days after vaccination 3. All-cause diarrhoea: gastroenteritis defined as diarrhoea characterized by ≥ 3 looser than normal stools within a day; minimum of 5 days required between episodes for them to be considered as separate events; measured during follow-up (2 years) 4. Severe all-cause diarrhoea: information on diary cards was used to assess the severity of each gastroenteritis episode according to a 20-point scoring system; measured during follow-up (2 years) 5. Rotavirus diarrhoea: all rotavirus-positive specimens were tested by reverse transcription-polymerase chain reaction at GlaxoSmithKline to determine the G type; any G1 rotavirus detected until 2 months after the second dose were analysed to differentiate between vaccine strain and wild G1 strains; only gastroenteritis episodes in which wild rotavirus other than the vaccine strain was identified in a stool specimen were included in the efficacy analysis; measured during follow-up (2 years) 6. Severe rotavirus diarrhoea: see above; measured during follow-up (2 years) 7. All-cause hospital admission: no definition; measured during follow-up (2 years) 8. All-cause mortality: no definition; measured during follow-up (2 years) 9. Rotavirus diarrhoea resulting in hospitalization **Outcomes to measure immunogenicity** 10. Vaccine take: rotavirus shedding in stool specimens [review includes data from day 7 after dose 2] 11. Seroconversion: "percentages of infants with post-antirotavirus IgA antibody concentration 20 units/mL in infants who were negative for rotavirus before the first dose of RIX4414 or placebo" [review includes data from 2 months after dose 1 and 2 months after dose 2]
Immunization status	Oral polio vaccine given after 2 weeks, not together with RV1
Location	Belem (Brazil), Mexico City (Mexico), Valencia (Venezuela) WHO mortality stratum B

Notes	**Date:** 25 May 2001 to 8 November 2003 **Source of funding:** GlaxoSmithKline Biologicals **Malnutrition:** reported in "Journal of Infectious Disease, 2007, 196(4): 537-40" **Other:** main publication did not report that the trial included 2 subsets: • 2 doses of human rotavirus or placebo subset: these participants received 2 oral doses of RV1 vaccine or placebo according to a 0, 2 months schedule, and routine vaccinations (DTPw- Hepatitis B vaccine (HBV) + Hib vaccine) at a 0, 2, and 4 months schedule • 3 doses of RV1 or placebo subset: these participants received 3 oral doses of RV1 vaccine or placebo, and routine vaccinations (DTPw-HBV + Hib vaccine) concomitantly with each dose of human rotavirus vaccine and placebo at a 0, 2, and 4 months schedule **Immunogenicity sampling:** "A subset of infants (N 800) provided blood samples 2 months after the first dose (serology for antirotavirus IgA antibodies) and 2 months after the second dose (serology for antirotavirus IgA antibodies and antibodies against antigens of routine infant vaccines). The first 200 enrolled infants in each participating country constituted this subset, and the remaining 200 infants were included according to the order of enrolment irrespective of country"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated; "The participating infants were randomly assigned to one of the 4 study groups (3 vaccine groups and a placebo group) following a 1:1:1:1 allocation ratio according to a computer-generated randomization list"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	"Double blinding was maintained during the entire study period"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	High risk	Not all pre-specified outcomes reported
Other bias	Unclear risk	GlaxoSmithKline final report stated that part of the population received 3 doses of rotavirus vaccine. This was not mentioned on the original published report

RV1 Steele 2008-ZAF

Methods	RCT **Length of follow-up:** up to 6 months after last vaccine given **Adverse event data collection methods:** "The infants were monitored for at least 30 min after each vaccination. Parents received a diary card to record information daily about solicited general symptoms (fever, fussiness/irritability, diarrhoea, vomiting, loss of appetite or cough/runny nose) for 15 days after each dose of RIX4414 or placebo, and any other adverse events occurring until the next study visit. Weekly supervision was done by Health Care Workers from Madibeng District Health Centre. The study physician or his staff questioned the parents on their child's health and verified the completed diary card at each visit
Participants	**Number:** 450 enrolled; 406 evaluable Two cohorts were vaccinated: 1st cohort before the rotavirus season (271 participants); 2nd cohort after the rotavirus season (179) participants **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants, born after a normal gestation period of ≥ 36 weeks; 5 to 10 weeks of age at the time of the first study visit; free of obvious health problems as established by medical history and clinical examination before entering into the study. There were no restrictions on feeding the infants before or after vaccination **Exclusion criteria**: infants were excluded if they had a clinically significant history of gastrointestinal disease or malformation, had received vaccines or treatment prohibited by the protocol, were immuno-compromised or were in household contact with an immuno-suppressed individual or pregnant woman. Bacillus Calmette-Guerin (BCG) and OPV vaccinations at birth were allowed according to the local EPI schedule. Vaccination was postponed if the infant had fever (≥37.5 C axillary or ≥38 C rectal) or gastroenteritis within the previous 7 days
Interventions	RV1 1. RIX4414 (RV1): 10^5 FFU; 2 doses given 1 month apart; 300 participants (randomized) 1.1. RV1 vaccine + oral polio vaccine + diphtheria-tetanus-acellular pertussis/*H. influenzae* type b vaccine 1.2. RV1 vaccine + oral polio vaccine placebo + diphtheria-tetanus-acellular pertussis inactivated polio-*H. influenzae* type b vaccine 1.3. RV1 placebo + diphtheria-tetanus-acellular pertussis inactivated polio-*H. influenzae* type b vaccine 2. Placebo: 2 doses given 1 month apart; 150 participants (randomized)
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity (see **Adverse event data collection methods** above) 2. Serious adverse events: Infants who experienced a serious adverse event and required hospitalization were admitted at the local district hospital in the study sites or at Ga-Rankuwa Hospital, the referral hospital for the study site and surrounding areas. Parents were informed on the symptoms of intussusception and were instructed to contact the study physician or clinic if any signs of intussusception became apparent. Any suspected cases were immediately referred to Ga-Rankuwa Hospital. All serious adverse events were reported to the sponsor and the Ethics committees and followed-up until resolved. Parents were contacted 6 months after the second dose of RIX4414 or placebo to obtain information on any serious adverse events since the final study visit. All serious adverse events were reviewed periodically by an independent

	safety monitoring committee 3. All-cause death 4. Drop-outs 5. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity** 6. Vaccine virus shedding: vaccine virus in stool sample (review includes data from combined time points) 7. Seroconversion: appearance of anti-rotavirus IgA antibody (concentration ≥ 20 U/mL) in participants negative for rotavirus before vaccination (review includes data from 289 participants)
Immunization status	Diphtheria-tetanus-acellular pertussis, polio virus, and *H. influenzae* type b co-administered in trial
Location	Madibeng District, North West Province, South Africa WHO mortality stratum E
Notes	**Date:** 1st cohort started from 22 November 2001; 2nd cohort from 23 October 2002 to 15 October 2003 **Source of funding:** The study (e-Track 444563-014/NCT00346892) was sponsored by a public-private partnership RAPID and GSK Biologicals. The RAPID partnership consists of public sector partners (including the WHO, US Agency for International Development, National Institutes of Health, Children's Vaccine Programme and the Centers for Disease Control), academic institutions (International Centre for Diarrhoeal Disease Research, Bangladesh and Medical University of Southern Africa) and GlaxoSmithKline Biologicals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Very likely; "This study was conducted under the WHO RAPID (Rotavirus Action Partnership for Immunization and Development) programme that facilitates conduct of rotavirus vaccine trials in developing countries, specifically in Africa and Asia, to address specific developing country needs. The RAPID partnership consists of public sector partners (including the WHO, US Agency for International Development, National Institutes of Health, Children's Vaccine Programme and the Centers for Disease Control), academic institutions (International Centre for Diarrhoeal Disease Research, Bangladesh and Medical University of Southern Africa) and GlaxoSmithKline Biologicals"

RV1 Steele 2008-ZAF (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No details; "balanced allocation (1:1:1)"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding of oral polio vaccine co-administration not completely blinded. "OPV and its placebo used in the first cohort were identical in appearance allowing for double blinding while this was not possible in the second cohort due to differences in appearance of OPV and its placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All infants who had received at least one dose of RIX4414 or placebo (total vaccinated cohort) were included in the primary analysis of reactogenicity"
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	Unclear risk	Funded by RAPID partnership and GlaxoSmithKline Biologicals. Protocol published a prior with ClinicalTrials.gov, number NCT00346892. "The public sector partners provided co-funding and technical expertise for clinical evaluation. GSK Biologicals supplied all vaccine doses, handled the study design, the collection and analysis of data, the monitoring and implementation of the study in collaboration with the study centres, which are WHO reference centres. In addition, GSK Biologicals also coordinated the report writing and took part in the decision to submit the paper for publication"

RV1 Steele 2010a-ZAF

Methods	RCT **Length of follow-up:** up to 31 days after each vaccine dose and 42 days after the last vaccine dose **Adverse event data collection methods:** all solicited general symptoms (fever, fussiness /irritability, diarrhoea, vomiting, loss of appetite, cough/runny nose) and unsolicited symptoms were recorded during the 15-day and 31-day postvaccination follow-up period after each RIX4414/placebo dose, respectively. The intensity of adverse events was assessed on a 4-point scale, where "0" indicated no symptoms; "1," mild; "2," moderate; and "3" severe symptoms. Symptoms of Grade 3 intensity were defined as follows: rectal temperature ≥39.5°C (fever), ≥6 looser than normal stools per day (diarrhoea), ≥3 episodes of vomiting per day (vomiting), refusing food intake (loss of appetite), and preventing normal activity (cough/runny nose, fussiness/irritability). Grade 2 symptoms were defined as rectal temperature of 38.5°C to 39.5°C (fever), 4 to 5 looser than normal stools/d (diarrhoea), 2 episodes of vomiting/d (vomiting), eating lesser than usual, which interfered with normal activity (loss of appetite), and interfering with normal activity (cough/runny nose, fussiness / irritability). Occurrence of SAEs was recorded throughout the study period
Participants	**Number:** 100 enrolled; 100 evaluable for safety, 50 for immunogenicity **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** only HIV-positive infants (confirmed at screening) who were clinically asymptomatic or mildly symptomatic (clinical stages I and II according to WHO classification) and aged 6 to 10 weeks at the time of Dose 1 of RIX4414/placebo were enrolled. There were no restrictions on feeding the infants before or after vaccination **Exclusion criteria**: infants were not included in the study if they were confirmed HIV negative, had received any other investigational drug or vaccine 30 days before receiving the first dose of study vaccine, or had a history of chronic gastroenteritis or previous documented rotavirus gastroenteritis
Interventions	1. RV1: 3 doses at least $10^{6.0}$ CCID50 viral concentration 2. Placebo
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity (see **Adverse event data collection methods** above) 2. All-cause diarrhoea; A GE episode was defined as diarrhoea (3 or more, loose than normal stools per day) with or without vomiting. Stool samples were collected on Days 0, 7, 15, and 22 of Doses 1 and 2 and on Days 0, 7, 15, 30, 45, and 60 of Dose 3 3. Rotavirus diarrhoea; measured from 1 week after second dose up to 2 months' follow-up 4. Serious adverse events: infants who experienced a serious adverse event and required hospitalization were admitted at the local district hospital in the study sites or at Ga-Rankuwa Hospital, the referral hospital for the study site and surrounding areas. Parents were informed on the symptoms of intussusception and were instructed to contact the study physician or clinic if any signs of intussusception became apparent. Any suspected cases were immediately referred to Ga-Rankuwa Hospital. All serious adverse events were reported to the sponsor and the Ethics committees and followed-up until resolved. Parents were contacted 6 months after the second dose of RIX4414 or placebo to obtain information on any serious adverse events since the final study visit. All serious adverse events were reviewed periodically by an independent safety monitoring committee

RV1 Steele 2010a-ZAF (*Continued*)

	5. All-cause death 6. Drop-outs **Outcomes to measure immunogenicity** 7. Vaccine take: defined as serum antirotavirus IgA concentration 20 U/mL in postvaccination sera or rotavirus vaccine shedding in any stool sample collected from Dose 1 to 2 months post-Dose 3 for infants initially negative for rotavirus 8. Seroconversion: appearance of anti-rotavirus IgA antibody (concentration $\geq$ 20 U/mL) in participants negative for rotavirus before vaccination (review includes data from 289 participants)
Immunization status	RV1 vaccine was concomitantly administered with 3 doses of combined diphtheria, tetanus and whole-cell pertussis, hepatitis B, and *H. influenzae* type b vaccine (TritanrixHepBHib) and OPV (PolioSabin)
Location	Pretoria, South Africa WHO mortality stratum E
Notes	**Registration number:** ISRCTN11877362/NCT00263666 **Source of funding:** RAPID trials (USA); WHO (Switzerland) and GlaxoSmithKline Biologicals For infants who developed clinical symptoms of HIV (WHO stages III or IV disease) anytime after enrolment, access to antiretroviral therapy (cotrimoxazole) according to the South African national guidelines was facilitated. Infants who needed treatment were referred to antiretroviral therapy centres by the investigators

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Very likely; "This study was conducted under the WHO RAPID (Rotavirus Action Partnership for Immunization and Development) programme that facilitates conduct of rotavirus vaccine trials in developing countries, specifically in Africa and Asia, to address specific developing country needs. The RAPID partnership consists of public sector partners (including the WHO, US Agency for International Development, National Institutes of Health, Children's Vaccine Programme and the Centers for Disease Control), academic institutions (International Centre for Diarrhoeal Disease Research, Bangladesh and Medical University of Southern Africa) and GlaxoSmithKline Biologicals"
Allocation concealment (selection bias)	Unclear risk	1:1 randomization, no further details

RV1 Steele 2010a-ZAF (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	"The placebo was similar to RIX4414 in appearance and contained the same constituents as the active vaccine except that it did not contain the vaccine virus"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All infants who had received at least one dose of RIX4414 or placebo (total vaccinated cohort) were included in the primary analysis of reactogenicity"
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	Unclear risk	Supported by research grants from the WHO (V27/181/173), the Program for Appropriate Technology in Health (PATH Grant GAV.1142-01-07211-SPS), the Norwegian Program for Development, Research and Higher Education research grant (PRO 48/2002), and the South African Medical Research Council. GlaxoSmithKline Biologicals was also the funding source and was involved in all stages of the study conduct and analysis. GSK Biologicals also took in charge all costs associated with the development and the publishing of the present manuscript. Protocol published a priori with ClinicalTrials.gov, number NCT00263666

RV1 Steele 2010b-ZAF

Methods	RCT **Length of follow-up:** up to 6 months after last dose of vaccine or placebo **Adverse event data collection methods:** "The infants were monitored for at least 30 min after each vaccination. Parents received a diary card to record information daily about solicited general symptoms (fever, fussiness/irritability, diarrhoea, vomiting, loss of appetite or cough/runny nose) for 15 days after each dose of RIX4414 or placebo, and any other adverse events occurring until the next study visit. Weekly supervision was done by Health Care Workers from Madibeng District Health Centre. The study physician or his staff questioned the parents on their child's health and verified the completed diary card at each visit
Participants	**Number:** 475 participants enrolled; 420 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants, born after a normal gestation period of $\geq$ 36 weeks; 6 to 10 weeks of age at the time of the first study visit; free of obvious health problems as established by medical history and clinical examination before entering into the study, and mothers had confirmed negative HIV status

	Exclusion criteria: infants were excluded if they had a clinically significant history of gastrointestinal disease or malformation, had received vaccines or treatment prohibited by the protocol, were immuno-compromised or were in household contact with an immuno-suppressed individual or pregnant woman. Bacillus Calmette-Guerin (BCG) and OPV vaccinations at birth were allowed according to the local EPI schedule. Infants with acute disease at the time of enrolment or gastroenteritis (diarrhoea) within 7 days before administration of the study vaccine were also excluded. In addition, vaccination was postponed if the infant had fever (≥37.5 °C axillary or ≥38 °C rectal) or gastroenteritis within the previous 7 days
Interventions	RV1 1. RIX4414 (RV1): at least $10^{6.0}$ PFU CCID50 1.1. 2 doses, 1 month apart (at 10 and 14 weeks) *plus* 1 dose of placebo (at 6 weeks); 190 participants (randomized) 1.2. 3 doses, 1 month apart (at 6, 10, and 14 weeks of age); 189 participants (randomized) 2. Placebo: 3 doses, 1 month apart (at 6, 10, and 14 weeks of age); 96 participants (randomized) **Schedule:** Visits 1 (Dose 1), 2 (Dose 2), 3 (Dose 3), 4 and 5 correspond to months 0, 1, 2, 4, and 8 to 11 in the schedule
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity: for each type of solicited symptom, occurrence of the symptom within the 15-day (days 0 to 14) solicited follow-up period after each dose; occurrence of unsolicited adverse events within 43 days (days 0 to 42) after each dose, according to MedDRA classification; measured up to 43 days after vaccine/placebo 2. Serious adverse events: occurrence throughout entire study period; measured up to 6 months 5. All-cause death: fatal adverse events measured up to 6 months 6. Drop-outs: measured up to 6 months 7. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity** 8. Viral shedding: presence of rotavirus in any stool sample (review includes data from combined time points (these combined data for 2 and 3 doses)) 9. Seroconversion: appearance of anti-rotavirus IgA antibody concentration ≥ 20 U/mL in participants negative for rotavirus before first dose (review includes data from 1 month after dose 1 and 2 months after dose 3)
Immunization status	Infants received routine vaccinations according to the local EPI schedule in South Africa. Bacille Calmette-Guerin and OPV vaccinations were given at birth; all other routine vaccinations (including diphtheria-tetanus toxoids-whole cell pertussis, hepatitis B, *H. influenzae* type b, and OPV) were administered concomitantly with the study vaccine. All of the infants received a dose of OPV concomitantly with each dose of study vaccine or placebo at all administration times
Location	7 centres in South Africa WHO mortality stratum E

Notes	Study known as *RIX GSK[013] 2007-AF* in previously published versions of this review **Date:** 5 September 2003 to 25 October 2004 **Source of funding:** GlaxoSmithKline Biologicals **Study rationale:** "The aim of this study was to determine if there was a difference in immune response between the two different schedules that were tested"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Very likely. This study was conducted under the auspices of WHO (eTrack 444563/013/NCT00383903)
Allocation concealment (selection bias)	Unclear risk	2:2:1 randomization, no further details
Blinding (performance bias and detection bias) All outcomes	Low risk	"The placebo was similar to RIX4414 in appearance and contained the same constituents as the active vaccine except that it did not contain the vaccine virus"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All infants who had received at least one dose of RIX4414 or placebo (total vaccinated cohort) were included in the primary analysis of reactogenicity"
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	Unclear risk	Supported by research grants from the WHO (V27/181/173), the Program for Appropriate Technology in Health (PATH Grant GAV.1142-01-07211-SPS), the Norwegian Program for Development, Research and Higher Education research grant (PRO 48/2002), and the South African Medical Research Council. GlaxoSmithKline Biologicals was also the funding source and was involved in all stages of the study conduct and analysis. GSK Biologicals also took in charge all costs associated with the development and the publishing of the present manuscript Protocol published a prior with ClinicalTrials.gov (eTrack 444563/013/NCT00383903)

RV1 Vesikari 2004a-FIN

Methods	RCT **Length of follow-up:** 8 to 30 days after each dose **Adverse event data collection methods:** diary cards provided to participants or participants' parents/guardians to record solicited general symptoms on the day of each vaccination and for 7 subsequent days (passive method)
Participants	**Number:** 192 enrolled; 178 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants, born after a normal gestation period of 36 to 42 weeks; 6 to 12 weeks of age at the time of the first dose of the study vaccination course; free of obvious health problems as established by medical history and clinical examination before entering into the study **Exclusion criteria**: participating in any other clinical trial; acute disease; history of allergic reaction to any vaccine component; history of chronic gastrointestinal disease or other serious medical condition; undergone immunosuppressive therapy; received antibiotics within 14 days preceding the study vaccine administration and during the first 7 days after vaccine administration; any confirmed or suspected immunosuppressive or immunodeficient condition, had received any immunoglobulin therapy or blood products before start or during the trial; abnormal stool pattern or household contact with an immunosuppressed individual or pregnant woman; for the infants, previous confirmed occurrence of rotavirus gastroenteritis
Interventions	RV1 1. RIX4414 (RV1) 1.1. $10^{4.1}$ PFU; 32 participants (randomized) 1.2. $10^{4.7}$ PFU; 64 participants (randomized) * 1.3. $10^{5.8}$ PFU; 32 participants (randomized) 2. Placebo: 64 participants (randomized) **Schedule:** 2 doses given 2 months apart **Half of infants receiving $10^{4.7}$ PFU of* RV1 *were tested with prior administration of Mylanta as buffer; in the other half vaccine was diluted in a buffer containing calcium carbonate* Feeding was not allowed for an hour before and after study vaccine administration
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Adverse events requiring discontinuation: no definition; measured at 31 days follow-up after each dose 2. Serious adverse events: no definition; measured at 31 days follow-up after each dose 3. Reactogenicity: no definition; measured at 31 days follow-up after each dose 4. Drop-outs: no definition; measured at 31 days follow-up after each dose 5. All-cause mortality: no definition; measured at 31 days follow-up after each dose **Outcomes to measure immunogenicity** 6. Rotavirus shedding in stool (review includes data from day 7 to 9 after dose 2) 7. Seroconversion: appearance of serum anti-rotavirus IgA antibody to rotavirus in post-vaccination sera at a titre of $\geq$ 20 U/mL in previously uninfected infants; measured in infants only (review includes data from 2 months after dose 1 and 1 month after dose 2)
Immunization status	Infant routine vaccinations were separated from the study vaccines by 2 weeks

RV1 Vesikari 2004a-FIN (*Continued*)

Location	2 centres in Finland WHO mortality stratum A
Notes	**Date:** 29 May to 18 December 2000 **Source of funding:** GlaxoSmithKline Biologicals Trial report also includes results for a study in adults and in previously rotavirus infected children; neither included in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"The study was performed under double-blind with respect to the groups within each study part"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Fourteen subjects did not complete the study including one infant from 10*4.7 FFU with Mylanta® group who failed to complete the study due to an unrelated SAE (allergic reaction to DTP vaccine)" "15 subjects were eliminated from ATP analysis for non-compliance with the protocol (nine subjects) or seropositivity before vaccination (six subjects)"
Selective reporting (reporting bias)	Unclear risk	No information
Other bias	Unclear risk	No information

RV1 Vesikari 2004b-FIN

Methods	RCT Unbalanced randomization (2:1) **Length of follow-up:** 1 and 2 years of follow-up are reported **Adverse event data collection methods:** to assess reactogenicity, parents recorded daily on diary cards rectal temperature, any diarrhoea, vomiting, irritability, and loss of appetite for 15 days after each vaccination. Any other symptoms or signs occurring during a 43-day follow-up period after each vaccination were recorded as unsolicited symptoms (or signs) (passive method)

Participants	**Number:** 405 enrolled; 372 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants, born after a normal gestation period of 36 to 42 weeks; 6 to 12 weeks of age at the time of the first dose of the study vaccination course; free of obvious health problems as established by medical history and clinical examination before entering into the study **Exclusion criteria**: premature labour; vaccination was delayed if infant had fever (rectal temperature > 38 °C) or had gastroenteritis within the previous 7 days
Interventions	RV1 1. RIX4414 (RV1): $10^{4.7}$ PFU; 2 doses given 2 months apart; 270 participants (randomized) 2. Placebo: 2 doses given 2 months apart; 135 participants (randomized) Feeding was not allowed for 1 h before administration of the study vaccine
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Rotavirus diarrhoea: occurrence of rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the first rotavirus season following vaccination as detected by reverse transcription-polymerase chain reaction (RT-PCR) in stool samples; occurrence of asymptomatic rotavirus infections during the period starting from 1 month after dose 2 until the end of each rotavirus season following vaccination; G type of the wild rotavirus strain by RT-PCR; measured at 1 year (first report) and 2 years (second report) 2. Reactogenicity: for each type of solicited symptom, occurrence of the symptom within the 15-day solicited follow-up period after each dose; measured at 15 days after each dose 3. Adverse events requiring discontinuation: occurrence of unsolicited symptoms within 42 days after each dose, according to WHO's classification; measured 42 days after each dose 4. Serious adverse events: no definition; measured at all follow-up 5. All-cause diarrhoea: gastroenteritis was defined as diarrhoea ($\geq$ 3 looser than normal stools within any day) and/or vomiting ($\geq$ 1 episodes of forceful emptying of partially digested stomach contents > 1 h after feeding within any day; 2 occurrences of gastroenteritis were classified as separate episodes if there were $\geq$ 5 symptom-free days between them 6. Severe rotavirus diarrhoea: score of < 7 prospectively defined as mild; score of 7 to 10 as moderate; and a score > 11 as severe 7. Rotavirus diarrhoea resulting in hospitalization 8. All-cause death 9. Drop outs **Outcomes to measure immunogenicity** 10. Seroconversion: anti-rotavirus antibody IgA concentration of $\geq$ 20 units/mL in infants negative for this before the first dose (review includes data from 1 month after dose 2)
Immunization status	Infant routine vaccinations (diphtheria tetanus toxoids-pertussis, *H. influenzae* type b, and inactivated poliovirus vaccines) were separated from the study vaccines by at least 2 weeks

Location	6 centres in Finland WHO mortality stratum A
Notes	**Date:** 21 August 2000 to 11 July 2002 **Source of funding:** GlaxoSmithKline Biologicals **Other:** GSK 444663/004 (rota-004annex) reports a second year extension of the study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Eligible infants were randomly assigned (2:1 ratio) to 2 study groups according to a computer-generated randomization list to receive the vaccine or placebo by mouth"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	"The placebo had the same constituents and identical appearance as the active vaccine, but did not contain the vaccine virus"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	44 subjects were eliminated from ATP analysis for non-compliance with the protocol (five subjects) or unknown rotavirus status (one subject) or reason not stated (38 subjects)
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	Unclear risk	No information

RV1 Vesikari 2007a-EU

Methods	RCT **Length of follow-up:** 1 and 2 years of follow-up in all countries, and a third year follow-up in Finland (GSK109810) **Adverse event data collection methods:** "active surveillance for gastroenteritis episodes and serious adverse events from the day of the first vaccine or placebo dose (8 September 2004) until the follow-up visit at the end of the second rotavirus epidemic season (10 August 2006) ... Study staff contacted parents every week" (active method); "During every episode, we asked parents to record in a daily diary card the number of looser than normal stools, axillary or rectal temperature, number of vomiting episodes, any rehydration or other medication administered, and any medical attention (defined as medical personnel contact, advice, or visit; emergency room contact or visit; or admission) " (passive method)
Participants	**Number:** 3994 enrolled; 3848 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants aged 6 to 14 weeks who weighed > 2000 g at birth **Exclusion criteria**: acute disease at the time of enrolment; history of chronic administration of immunosuppressants since birth; received any vaccines or treatments prohibited by the protocol; or had any disorders or illnesses excluded by the protocol
Interventions	RV1 1. RIX4414 (RV1): $10^{6.5}$ PFU; 2 doses given 1 or 2 months apart; 2646 participants (randomized) 2. Placebo: 2 doses given 1 or 2 months apart; 1348 participants (randomized)
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. All-cause diarrhoea: gastroenteritis defined as diarrhoea characterized by at least 3 looser than normal stools within a day, with or without vomiting; measured 2 weeks after dose 2 until end of 2 years follow-up 2. Rotavirus diarrhoea: trialists deemed a gastroenteritis episode to be caused by rotavirus if a rotavirus strain was identified in a stool sample collected during the episode or within 7 days after resolution of symptoms, or before the next episode if fewer than 7 days had fallen between the end of 1 episode and the start of the next, in cases of multiple episodes; measured 2 weeks after dose 2 until end of 2 years follow-up 3. Severe rotavirus diarrhoea: score < 7 was defined prospectively as mild, score of 7 to 10 as moderate, and a score of ≥ 11 as severe 4. Severe all-cause diarrhoea: as for severe rotavirus diarrhoea 5. Emergency department visit: no definition 6. All-cause hospitalization admission: no definition 7. Serious adverse events: no definition 8. Rotavirus diarrhoea resulting in hospitalization 9. Rotavirus diarrhoea requiring medical attention (defined as "medical personnel contact, advice, or visit; emergency room contact or visit; or admission") 10. Reactogenicity **Outcomes to measure immunogenicity** 11. Seroconversion: appearance of anti-rotavirus IgA antibody concentration ≥ 20 U/mL in participants seronegative for rotavirus before vaccination (review includes data from 1 to 2 months after dose 2)

Immunization status	Concomitant vaccines included 7 valent pneumococcal polysaccharide conjugate vaccine (Prevenar) and meningococcal group c conjugate vaccine (Meningitec); Hepatitis B vaccine, diphtheria-tetanus-acellular pertussis, polio virus, and *H. influenzae* type b vaccines were co-administered
Location	98 centres in six European countries (Czech Republic, Finland, France, Germany, Italy, and Spain) WHO mortality stratum A
Notes	**Date:** 12 February 2007 to 08 August 2007 **Source of funding:** funded by GlaxoSmithKline Biologicals **Other:** vaccination postponed if baby either had a temperature of $\geq$ 37.5 °C (axillary) or of 38.0 °C (rectal) or had gastroenteritis within 7 days before planned vaccination **Study aim:** "to assess the efficacy and safety of HRV [RV1] vaccine during the 3rd year of age in subjects primed with a 2-dose schedule in study 102247, with the first dose administered at the age of 6 to 14 weeks"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"GSK Biologicals provided vaccine supplies that were numbered with a computer-generated randomization list"
Allocation concealment (selection bias)	Low risk	"randomization was done by a central Internet randomization system. Infants were randomly allocated in a 2/1 ratio two doses of either RIX4414 or placebo"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Treatment allocation remained concealed from investigators and the parents of participating infants throughout the study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data imputed appropriately
Selective reporting (reporting bias)	Unclear risk	Data are provided only rotavirus gastroenteritis and for severe gastroenteritis, not for all gastroenteritis episodes
Other bias	Unclear risk	No information

RV1 Vesikari 2011-FIN

Methods	RCT **Length of follow-up:** 2 months **Adverse event data collection methods:** passive. "Parents/guardians of infants were provided diary cards to record solicited general symptoms (loss of appetite, fussiness/ irritability, fever, diarrhoea, vomiting, and cough/runny nose) during a 15-day post-vaccination follow-up period. The intensity of each adverse event was assessed using a 4-point scale where "0" refers to 'absent' and "3" refers to 'severe"'
Participants	**Number:** 250 enrolled and randomized; ATP safety cohort: 240; ATP immunogenicity cohort: 237 **Inclusion criteria:** healthy infants aged 6 to 10 weeks with a birth weight > 2 kg **Exclusion criteria:** any other investigational drug or vaccine 30 days prior to the administration of the first dose of the study vaccine; a history of allergy; rotavirus gastroenteritis; infants with acute illness at the time of enrolment could not receive the vaccine until the condition was resolved
Interventions	1. Liquid formulation of RIX4414*/(RV1), 1.5 mL 2. Placebo corresponding to liquid vaccine formulation 3. Lyophilized formulation RIX4414*/(RV1), 1 mL 4. Placebo corresponding to lyophilized vaccine formulation * vaccine containing at least 10^6 median $CCID_{50}$ of live attenuated RIX4414 human rotavirus strain **Schedule:** 2 oral doses at month 0 and 1 (minimum time interval between doses: 14 days)
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity, occurrence of the symptom within the 15-day solicited follow-up period after each dose (collected from GSK report) 2. Serious adverse events, occurrence throughout study period 3. * Rotavirus diarrhoea, stool samples collected during diarrhoea episodes tested for rotavirus strains 4. * All-cause diarrhoea, up to 1 month post dose 2 5. Drop outs: up to 2 months after dose 2 (collected from GSK report) 6. All-cause death (collected from GSK report) 7. Adverse events resulting in discontinuation (collected from GSK report) **Outcomes to measure immunogenicity** 8. Seroconversion, antirotavirus IgA antibody concentration > 20 U/mL, 1 month after each dose (collected from GSK report) 9. Rotavirus vaccine virus shedding in stools, reported at peak (day 7 post dose 1) * Outcome reported as proportion (P) with 95% CI. Events (n) and totals (N) were estimated by using the value when two formulas for the standard error (SE) converged
Immunization status	Routine childhood vaccinations were allowed according to local practice, but at least 14 days apart from each dose of study vaccine
Location	Five centres in Finland WHO mortality stratum A

Notes	Study known as *RIX GSK[048] 2007-EU* in previously published versions of this review **Date:** August to November 2005 **Source of funding:** GlaxoSmithKline Biologicals **Study rationale:** the immunogenicity, reactogenicity and safety of the RV1 liquid formulation were compared with lyophilized formulation and placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated "A standard SAS® program was used for generating the randomization list and a block randomization was used in order to ensure that the balance between the treatment arms were maintained"
Allocation concealment (selection bias)	Unclear risk	Unique treatment number "A unique treatment number identified the vaccine/placebo doses that were to be administered to the infants". No details reported how allocation of treatment number was concealed
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and key personnel were blinded as far as technically possible. "The study was double blind with respect to each of the vaccine formulation and their respective placebo; however, blinding between the two vaccine formulations was not technically possible because of the difference in appearance of the vaccines"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition balanced across study groups with reasons for drop-out/exclusion reported
Selective reporting (reporting bias)	Low risk	All pre-published outcomes reported
Other bias	Unclear risk	Funded by GlaxoSmithKline Biologicals

RV1 Ward 2006-USA

Methods	RCT **Length of follow-up:** 7 days following each vaccination; 3 to 5 weeks after second vaccination **Adverse event data collection methods:** unclear
Participants	**Number:** 117 enrolled; 111 evaluable **Age range:** 3 to 6 months (beginning); 3 to 6 months (end) **Inclusion criteria:** not specified **Exclusion criteria:** not specified
Interventions	RV1 1. RIX4414 (RV1) 1.1. 1 x 10^5 dose; 41 participants (randomized) 1.2. 1 x 10^6 dose; 39 participants (randomized) 2. Placebo: 37 participants **Schedule:** 2 doses given at a 6 to 10 week interval
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity*: symptoms of rotavirus illness, including fever, diarrhoea, and vomiting; measured for 7 days after each dose **Although mentioned in the methods, no results are presented* **Outcomes to measure immunogenicity** 2. Vaccine take: faecal shedding of rotavirus antigen (review includes data from after either dose 1 or 2) 3. Seroconversion: serum rotavirus IgA responses (increases in level of serum rotavirus IgA $\geq$ 4 fold) (review includes data from after either dose 1 or 2)
Immunization status	Not specified
Location	Cincinnati and Baltimore, USA WHO mortality stratum A
Notes	**Date:** July to December 1996 **Source of funding:** "Avant Immunotherapeutics, to which the 89-12 vaccine candidate was licensed and which sublicensed its product to GlaxoSmithKline (which developed Rotarix from 89-12)." 89-12 was the precursor to RV1

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	"double-blinded, placebo-controlled study designed"

RV1 Ward 2006-USA (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	"double-blinded, placebo-controlled study designed"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No impact on intervention effect estimate; "Of the 80 vaccine recipients in this trial, 2 had evidence of natural rotavirus infection before administration of the first dose, determined on the basis of rotavirus IgA in their serum. These, along with the 3 who received only 1 dose of vaccine, were eliminated from further analyses"
Selective reporting (reporting bias)	Unclear risk	No information
Other bias	Unclear risk	No information

RV1 Zaman 2009-BGD

Methods	RCT **Length of follow-up:** 31 days after each vaccination (total of 14 weeks) **Adverse event data collection methods:** "active surveillance for reactogenicity and safety was conducted via daily home visits by study personnel for 8 days after each dose of vaccine or placebo dose and bi-weekly home visits thereafter until one month after last dose" (active method); "During every episode, parents were asked to record in a daily diary card the number of looser than normal stools, axillary or rectal temperature, number of vomiting episodes, any rehydration or other medication administered, and any medical attention (defined as medical personnel contact, advice, or visit; emergency room contact or visit; or admission)" (passive method); serious adverse events were reviewed periodically by an independent committee
Participants	**Number:** 300 enrolled; 290 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants aged 6 to 7 weeks **Exclusion criteria**: acute disease at the time of enrolment; malnourished children; history of chronic administration of immunosuppressants since birth; received any vaccines or treatments prohibited by the protocol; or had any disorders or illnesses excluded by the protocol
Interventions	RV1 1. RIX4414 (RV1) 1.1. 1 x $10^{6.5}$ dose + OPV; 100 participants (randomized) 1.2. 1 x $10^{6.5}$ dose; 100 participants (randomized) 2. Placebo: 2.1. Placebo + OPV; 50 participants (randomized) 2.2. Placebo; 50 participants (randomized) **Schedule:** 2 doses given at a 6 to 12 week interval

Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity: for each type of solicited symptom, occurrence of the symptom within the 8 day (Day 0 to 7) solicited follow-up period after each dose; occurrence of unsolicited adverse events within 31 days (Day 0 to 30) after each dose, according to MedDRA classification; measured up to 31 days after vaccine/placebo 2. Serious adverse events: occurrence throughout entire study period (up to 105 days after vaccine/placebo) 3. Drop outs: measured up to 105 days after vaccine/placebo 4. Rotavirus diarrhoea: presence of rotavirus in gastroenteritis episode stools collected from dose 1 of vaccine/placebo up to 2 months after dose 2; measured up to 105 days after vaccine/placebo 5. All-cause death 6. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity** 7. Viral shedding: % participants with rotavirus antigen in stool samples collected at predetermined time points (ATP cohort for immunogenicity, stool analysis subset) (review includes data from combined time points) 8. Seroconversion: appearance of anti-rotavirus immunoglobulin A antibody concentration $\geq$ 20 U/mL in participants who were negative for rotavirus before vaccination (review includes data from 1 month after dose 2)
Immunization status	All children in the study received the standard EPI vaccines starting at 6 weeks of age, including oral polio vaccine for one RV1 vaccine arm and one placebo arm
Location	Single site in urban Dhaka at Mirpur, Bangladesh WHO mortality stratum D
Notes	**Date:** June 2005 to January 2006 **Source of funding:** funded by GlaxoSmithKline Biologicals and the Rotavirus Vaccine Program (RVP) at the Program for Appropriate Technology in Health (PATH)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	"double-blinded, placebo-controlled study designed"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"double-blinded, placebo-controlled study designed"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data imputed appropriately

RV1 Zaman 2009-BGD (*Continued*)

Selective reporting (reporting bias)	Unclear risk	No information
Other bias	Unclear risk	No information

RV5 Armah 2010-AF

Methods	RCT **Length of follow-up:** up to 43 days for safety outcomes, and up to 21 months for efficacy outcomes **Adverse event data collection methods:** "Study physicians reported and documented all serious adverse events occurring within 14 days of any dose and deaths or vaccine-related serious adverse events occurring at any time during the study" A subset had active surveillance: "A subset of 300 participants enrolled in Kenya was followed up for 42 days for all adverse events, including vomiting, diarrhoea, and high temperature. Home visits were attempted on days 3, 5, 7, 14, 21, and 42 after all vaccinations"
Participants	**Number:** 5560 enrolled; 5468 randomized, 5225 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants aged 4 to 12 weeks; "no symptoms of active gastrointestinal disease and could be adequately followed up for safety by home visit or telephone contact (1 week and 2 weeks after any dose of vaccine or placebo)"; breastfeeding was not restricted; no enrolment restrictions based on HIV status - infants in Kenya were offered routine HIV testing, and a subset were followed up for safety All children exposed to or infected with HIV were referred for appropriate HIV care and treatment; voluntary counselling and testing were also offered to mothers of infants exposed to HIV **Exclusion criteria**: see above **Special group:** HIV-infected participants
Interventions	RV5 1. WC3 (RV5): 2 mL (every dose had an estimated potency of 10^7 infectious units per reassortant rotavirus); 3 doses given 4 weeks apart; 2733 participants (randomized) 2. Placebo: 2 mL; 3 doses given 4 weeks apart; 2735 participants (randomized) **Schedule:** 3 doses given at a 4-week interval
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Serious adverse events (including intussusception) 2. Death due to serious adverse events 3. Rotavirus diarrhoea: case definition for rotavirus gastroenteritis required participants to meet both of the following criteria: (1) $\geq$ 3 watery or looser-than-normal stools within a 24-h period and/or forceful vomiting, and (2) rotavirus detected by enzyme immunoassay (EIA) in a stool specimen taken within 14 days after the onset of symptoms 4. Severe rotavirus diarrhoea: an established clinical scoring system based on the intensity and duration of fever, vomiting, diarrhoea, and changes in behaviour used to categorize episodes of rotavirus gastroenteritis on a 20-point severity scale; scores > 11 were considered to indicate severe disease; measured up to 2 years follow-up 5. All-cause diarrhoea

	6. All-cause diarrhoea - severe 7. Reactogenicity*: symptoms of rotavirus illness, including fever, diarrhoea, and vomiting; measured for 7 days after each dose (review includes data from for the end of follow-up) **Data on fever and vomiting are provided only on figure 2 and data could not be extracted reliably* **Outcomes to measure immunogenicity** 8. Seroconversion: serum rotavirus IgA responses (increases in level of serum rotavirus IgA ≥ 4 fold) (review includes data from after dose 2)
Immunization status	All children in the study received the standard EPI vaccines (including oral poliovirus vaccine) starting at 6 weeks of age
Location	Sites in rural Kassena-Nankana district (Ghana), rural Karemo division, Siaya district (Kenya), and urban area of Bamako (Mali) WHO mortality strata D, E
Notes	This trial was conducted in Ghana, Kenya and Mali, data reported separately per country can be found under RV5 Armah 2010-GHA; RV5 Armah 2010-KEN and RV5 Armah 2010-MLI. **Date:** 28 April 2007 to 31 March 2009 **Source of funding:** funded by PATH (GAVI Alliance grant) and Merck **Registration number:** NCT00362648

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Unique allocation numbers were designated at Merck as pentavalent rotavirus vaccine or placebo with computer generated block randomization, with block sizes of six"
Allocation concealment (selection bias)	Low risk	"Vaccine and placebo packages were then labelled with allocation numbers and provided to sites in identical presentations. Sites were instructed to assign allocation numbers to participants in sequential order as they were enrolled"
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and staff: "Participants were enrolled by study staff, who remained masked to treatment assignment throughout the trial" Researchers: "The statistician from Merck who analysed the data and the Merck and PATH protocol teams were masked to treatment assignment"

RV5 Armah 2010-AF (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes reported
Other bias	Low risk	Funded by PATH (GAVI Alliance grant) and Merck. Protocol published a prior with ClinicalTrials.gov, number NCT00362648. "The study was designed by scientists from Merck, with substantial input from PATH staff and site investigators. Merck had direct oversight or participation in every stage of the study. Merck also participated in pharmacovigilance, organised and led the data and safety monitoring board meetings, and did the data analysis. Staff from PATH independently monitored study execution at sites and participated in pharmacovigilance, data analysis, and data and safety monitoring board meetings. All authors had full access to the data, and the corresponding author had final responsibility for the decision to submit for publication"

RV5 Armah 2010-GHA

Methods	RCT **Length of follow-up:** up to 43 days for safety outcomes, and up to 21 months for efficacy outcomes **Adverse event data collection methods:** "Study physicians reported and documented all serious adverse events occurring within 14 days of any dose and deaths or vaccine-related serious adverse events occurring at any time during the study"
Participants	**Number:** 2200 randomized **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants aged 4 to 12 weeks; "no symptoms of active gastrointestinal disease and could be adequately followed up for safety by home visit or telephone contact (1 week and 2 weeks after any dose of vaccine or placebo)"; breastfeeding was not restricted; no enrolment restrictions based on HIV status All children exposed to or infected with HIV were referred for appropriate HIV care and treatment; voluntary counselling and testing were also offered to mothers of infants exposed to HIV **Exclusion criteria**: see above
Interventions	RV5 1. WC3 (RV5): 2 mL (every dose had an estimated potency of 10^7 infectious units per reassortant rotavirus); 3 doses given 4 weeks apart; 1098 participants (randomized)

	2. Placebo: 2 mL; 3 doses given 4 weeks apart; 1102 participants (randomized) **Schedule:** 3 doses given at a 4-week interval
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Serious adverse events (including intussusception) 2. Death due to serious adverse events 3. Rotavirus diarrhoea: case definition for rotavirus gastroenteritis required participants to meet both of the following criteria: (1) ≥ 3 watery or looser-than-normal stools within a 24-h period and/or forceful vomiting, and (2) rotavirus detected by EIA in a stool specimen taken within 14 days after the onset of symptoms 4. Severe rotavirus diarrhoea: an established clinical scoring system based on the intensity and duration of fever, vomiting, diarrhoea, and changes in behaviour used to categorize episodes of rotavirus gastroenteritis on a 20-point severity scale; scores > 11 were considered to indicate severe disease; measured up to 2 years follow-up 5. All-cause diarrhoea 6. All-cause diarrhoea - severe 7. Reactogenicity*: symptoms of rotavirus illness, including fever, diarrhoea, and vomiting; measured for 7 days after each dose [review includes data from for the end of follow-up] **Data on fever and vomiting are provided only on figure 2 and data could not be extracted reliably* **Outcomes to measure immunogenicity** 8. Seroconversion: serum rotavirus IgA responses (increases in level of serum rotavirus IgA ≥ 4 fold) (review includes data from after dose 2)
Immunization status	All children in the study received the standard EPI vaccines (including oral poliovirus vaccine) starting at 6 weeks of age
Location	Sites in rural Kassena-Nankana district, Ghana WHO mortality stratum D
Notes	This trial was conducted in Ghana, Kenya and Mali, this part presents data for the Ghana cohort, data reported separately for the other countries can be found under RV5 Armah 2010-KEN and RV5 Armah 2010-MLI data reported for all countries under RV5 Armah 2010-AF **Date:** 28 April 2007 to 31 March 2009 **Source of funding:** funded by PATH (GAVI Alliance grant) and Merck **Registration number:** NCT00362648

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Unique allocation numbers were designated at Merck as pentavalent rotavirus vaccine or placebo with computer generated block randomization, with block sizes of six"

RV5 Armah 2010-GHA (*Continued*)

Allocation concealment (selection bias)	Low risk	"Vaccine and placebo packages were then labelled with allocation numbers and provided to sites in identical presentations. Sites were instructed to assign allocation numbers to participants in sequential order as they were enrolled"
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and staff: "Participants were enrolled by study staff, who remained masked to treatment assignment throughout the trial" Researchers: "The statistician from Merck who analysed the data and the Merck and PATH protocol teams were masked to treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes reported
Other bias	Low risk	Funded by PATH (GAVI Alliance grant) and Merck. Protocol published a prior with ClinicalTrials.gov, number NCT00362648. "The study was designed by scientists from Merck, with substantial input from PATH staff and site investigators. Merck had direct oversight or participation in every stage of the study. Merck also participated in pharmacovigilance, organised and led the data and safety monitoring board meetings, and did the data analysis. Staff from PATH independently monitored study execution at sites and participated in pharmacovigilance, data analysis, and data and safety monitoring board meetings. All authors had full access to the data, and the corresponding author had final responsibility for the decision to submit for publication"

RV5 Armah 2010-KEN

Methods	RCT **Length of follow-up:** up to 43 days for safety outcomes, and up to 21 months for efficacy outcomes **Adverse event data collection methods:** "Study physicians reported and documented all serious adverse events occurring within 14 days of any dose and deaths or vaccine-related serious adverse events occurring at any time during the study" A subset had active surveillance: "A subset of 300 participants enrolled in Kenya was followed up for 42 days for all adverse events, including vomiting, diarrhoea, and high temperature. Home visits were attempted on days 3, 5, 7, 14, 21, and 42 after all vaccinations"
Participants	**Number:** 5560 enrolled; 5468 randomized, 5225 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants aged 4 to 12 weeks; "no symptoms of active gastrointestinal disease and could be adequately followed up for safety by home visit or telephone contact (1 week and 2 weeks after any dose of vaccine or placebo)"; breastfeeding was not restricted; no enrolment restrictions based on HIV status - infants in Kenya were offered routine HIV testing, and a subset were followed up for safety All children exposed to or infected with HIV were referred for appropriate HIV care and treatment; voluntary counselling and testing were also offered to mothers of infants exposed to HIV **Exclusion criteria**: see above **Special group:** HIV-infected participants
Interventions	RV5 1. WC3 (RV5): 2 mL (every dose had an estimated potency of 10^7 infectious units per reassortant rotavirus); 3 doses given 4 weeks apart; 656 participants (randomized) 2. Placebo: 2 mL; 3 doses given 4 weeks apart; 652 participants (randomized) **Schedule:** 3 doses given at a 4 week interval
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Serious adverse events (including intussusception) 2. Death due to serious adverse events 3. Rotavirus diarrhoea: case definition for rotavirus gastroenteritis required participants to meet both of the following criteria: (1) $\geq$ 3 watery or looser-than-normal stools within a 24-h period and/or forceful vomiting, and (2) rotavirus detected by EIA in a stool specimen taken within 14 days after the onset of symptoms 4. Severe rotavirus diarrhoea: an established clinical scoring system based on the intensity and duration of fever, vomiting, diarrhoea, and changes in behaviour used to categorize episodes of rotavirus gastroenteritis on a 20-point severity scale; scores > 11 were considered to indicate severe disease; measured up to 2 years follow-up 5. All-cause diarrhoea 6. All-cause diarrhoea - severe 7. Reactogenicity*: symptoms of rotavirus illness, including fever, diarrhoea, and vomiting; measured for 7 days after each dose [review includes data from for the end of follow-up] **Data on fever and vomiting are provided only on figure 2 and data could not be extracted reliably* **Outcomes to measure immunogenicity**

	8. Seroconversion: serum rotavirus IgA responses (increases in level of serum rotavirus IgA ≥ 4 fold) (review includes data from after dose 2)
Immunization status	All children in the study received the standard EPI vaccines (including oral poliovirus vaccine) starting at 6 weeks of age
Location	Sites in rural Karemo division, Siaya district, Kenya WHO mortality stratum E
Notes	This trial was conducted in Ghana, Kenya and Mali, this part presents data for the Kenya cohort, data reported separately for the other countries can be found under RV5 Armah 2010-GHA and RV5 Armah 2010-MLI data reported for all countries under RV5 Armah 2010-AF **Date:** 28 April 2007 to 31 March 2009 **Source of funding:** funded by PATH (GAVI Alliance grant) and Merck **Registration number:** NCT00362648

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Unique allocation numbers were designated at Merck as pentavalent rotavirus vaccine or placebo with computer generated block randomization, with block sizes of six"
Allocation concealment (selection bias)	Low risk	"Vaccine and placebo packages were then labelled with allocation numbers and provided to sites in identical presentations. Sites were instructed to assign allocation numbers to participants in sequential order as they were enrolled"
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and staff: "Participants were enrolled by study staff, who remained masked to treatment assignment throughout the trial" Researchers: "The statistician from Merck who analysed the data and the Merck and PATH protocol teams were masked to treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes reported

RV5 Armah 2010-KEN (*Continued*)

Other bias	Low risk	Funded by PATH (GAVI Alliance grant) and Merck. Protocol published a prior with ClinicalTrials.gov, number NCT00362648. "The study was designed by scientists from Merck, with substantial input from PATH staff and site investigators. Merck had direct oversight or participation in every stage of the study. Merck also participated in pharmacovigilance, organised and led the data and safety monitoring board meetings, and did the data analysis. Staff from PATH independently monitored study execution at sites and participated in pharmacovigilance, data analysis, and data and safety monitoring board meetings. All authors had full access to the data, and the corresponding author had final responsibility for the decision to submit for publication"

RV5 Armah 2010-MLI

Methods	RCT **Length of follow-up:** up to 43 days for safety outcomes, and up to 21 months for efficacy outcomes **Adverse event data collection methods:** "Study physicians reported and documented all serious adverse events occurring within 14 days of any dose and deaths or vaccine-related serious adverse events occurring at any time during the study"
Participants	**Number:** 5560 enrolled; 5468 randomized, 5225 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants aged 4 to 12 weeks; "no symptoms of active gastrointestinal disease and could be adequately followed up for safety by home visit or telephone contact (1 week and 2 weeks after any dose of vaccine or placebo)"; breastfeeding was not restricted; no enrolment restrictions based on HIV status All children exposed to or infected with HIV were referred for appropriate HIV care and treatment; voluntary counselling and testing were also offered to mothers of infants exposed to HIV **Exclusion criteria**: see above
Interventions	RV5 1. WC3 (RV5): 2 mL (every dose had an estimated potency of 10^7 infectious units per reassortant rotavirus); 3 doses given 4 weeks apart; 979 participants (randomized) 2. Placebo: 2 mL; 3 doses given 4 weeks apart; 981 participants (randomized) **Schedule:** 3 doses given at a 4 week interval

Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Serious adverse events (including intussusception) 2. Death due to serious adverse events 3. Rotavirus diarrhoea: case definition for rotavirus gastroenteritis required participants to meet both of the following criteria: (1) ≥ 3 watery or looser-than-normal stools within a 24-h period and/or forceful vomiting, and (2) rotavirus detected by EIA in a stool specimen taken within 14 days after the onset of symptoms 4. Severe rotavirus diarrhoea: an established clinical scoring system based on the intensity and duration of fever, vomiting, diarrhoea, and changes in behaviour used to categorize episodes of rotavirus gastroenteritis on a 20-point severity scale; scores > 11 were considered to indicate severe disease; measured up to 2 years follow-up 5. All-cause diarrhoea 6. All-cause diarrhoea - severe 7. Reactogenicity *: symptoms of rotavirus illness, including fever, diarrhoea, and vomiting; measured for 7 days after each dose [review includes data from for the end of follow-up] ** Data on fever and vomiting are provided only on figure 2 and data could not be extracted reliably* **Outcomes to measure immunogenicity** 8. Seroconversion: serum rotavirus IgA responses (increases in level of serum rotavirus IgA ≥ 4 fold) (review includes data from after dose 2)
Immunization status	All children in the study received the standard EPI vaccines (including oral poliovirus vaccine) starting at 6 weeks of age
Location	Sites in urban area of Bamako, Mali WHO mortality stratum D
Notes	This trial was conducted in Ghana, Kenya and Mali, this part presents data for the Mali cohort **Date:** 28 April 2007 to 31 March 2009 **Source of funding:** funded by PATH (GAVI Alliance grant) and Merck **Registration number:** NCT00362648

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Unique allocation numbers were designated at Merck as pentavalent rotavirus vaccine or placebo with computer generated block randomization, with block sizes of six"
Allocation concealment (selection bias)	Low risk	"Vaccine and placebo packages were then labelled with allocation numbers and provided to sites in identical presentations. Sites were instructed to assign allocation

RV5 Armah 2010-MLI (*Continued*)

		numbers to participants in sequential order as they were enrolled"
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and staff: "Participants were enrolled by study staff, who remained masked to treatment assignment throughout the trial" Researchers: "The statistician from Merck who analysed the data and the Merck and PATH protocol teams were masked to treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	Funded by PATH (GAVI Alliance grant) and Merck. Protocol published a prior with ClinicalTrials.gov, number NCT00362648. "The study was designed by scientists from Merck, with substantial input from PATH staff and site investigators. Merck had direct oversight or participation in every stage of the study. Merck also participated in pharmacovigilance, organised and led the data and safety monitoring board meetings, and did the data analysis. Staff from PATH independently monitored study execution at sites and participated in pharmacovigilance, data analysis, and data and safety monitoring board meetings. All authors had full access to the data, and the corresponding author had final responsibility for the decision to submit for publication"

RV5 Block 2007-EU/USA

Methods	RCT **Length of follow-up:** up to 42 days for safety/immunogenicity; up to 1 year for efficacy **Adverse event data collection methods:** parents or guardians contacted by the study site on day 7, day 14, and day 42 after each vaccination and asked about serious adverse events (active method); parents or guardians were provided diary cards and were instructed to record daily temperatures for the infant for 7 days after each vaccination (passive method)
Participants	**Number:** 1312 enrolled; 1200 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end)

	Inclusion criteria: healthy infants, 6 through 12 weeks of age, who had no known history of congenital abdominal disorders, intussusception, or abdominal surgery; no known or suspected impairment of immunological function; no known hypersensitivity to any component of the rotavirus vaccine; no prior receipt of any rotavirus vaccine; no fever, with a rectal temperature ≥ 38.1 °C (≥ 100.5 °F) at the time of immunization; no history of known prior rotavirus disease, chronic diarrhoea, or failure to thrive; no clinical evidence of active gastrointestinal illness; no receipt of intramuscular, oral, or intravenous corticosteroid treatment within the 2 weeks before vaccination; did not reside in a household with an immunocompromised person; no prior receipt of a blood transfusion or blood products, including immunoglobulins; no receipt of oral poliovirus vaccine during the course of the study or within 42 days before first dose of vaccine/placebo; any infant who could not be adequately followed for safety by telephone or home visit; and no condition, which, in the opinion of the investigator, may have interfered with the evaluation of the study objectives **Exclusion criteria:** see above
Interventions	RV5 1. WC3 (RV5): 1.1 x 10^7 PFU; 651 participants (randomized) 2. Placebo: 661 participants (randomized) **Schedule:** 3 doses given 4 to 10 weeks apart
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Serious adverse events: potential cases of intussusception were adjudicated by an independent blinded committee; all study personnel remained blinded to the treatment arm and adjudication results of the potential intussusception cases; data on cases of intussusception, deaths, or other serious adverse events determined to be vaccine-related by the investigator were collected throughout the trial; measured up to 42 days, and up to 1 year (for vaccine-related serious adverse events) 2. Reactogenicity: no definition; measured up to 42 days 3. Drop outs: no definition: measured up to 1 year 4. Rotavirus diarrhoea: case of rotavirus gastroenteritis defined as meeting both of the following criteria: (a) > 3 watery or looser than normal stools within a 24-h period and/or forceful vomiting; and (b) rotavirus antigen detection by EIA in the stool sample. Primary analysis of efficacy included only cases caused by naturally occurring rotavirus of serotypes G1, G2, G3, or G4 as confirmed by reverse-transcriptase polymerase chain reaction (RT-PCR) occurring at least 14 days after the third dose 5. Severe rotavirus diarrhoea: each episode graded on a 24-point scale, where a score < 8 designated as mild, > 8 as moderate-and-severe, and > 16 as a severe disease 6. All-cause death 7. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity** 8. Seroconversion: pre-vaccination and post-vaccination sera analysed for serotype-specific rotavirus neutralizing antibody and for serum anti-rotavirus immunoglobulin A (IgA) (review includes data from after dose 3)
Immunization status	Use of oral poliovirus vaccine during the course of the study or within 42 days before first dose of vaccine/placebo was an exclusion criterion; administration of other vaccines permitted

RV5 Block 2007-EU/USA (*Continued*)

Location	30 sites; 27 in USA, and 3 in Finland WHO mortality stratum A
Notes	**Date:** 24 September 2002 (first patient in) to 11 February 2004 **Source of funding:** Merck & Co., Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Enrolled infants were randomly assigned 1:1 by using computer-generated allocation schedules to receive either vaccine or visibly indistinguishable placebo in a sucrose citrate buffer administered orally as three 2-mL doses 4 to 10 weeks apart"
Allocation concealment (selection bias)	Low risk	Sequential identical containers (see quote above)
Blinding (performance bias and detection bias) All outcomes	Low risk	"This randomized, clinical trial blinded to investigator, parent or guardian, and sponsor" "The placebo was identical to the vaccine except that it did not contain the rotavirus reassortants or trace trypsin"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	High risk	Key expected outcome (episodes of gastroenteritis) not included
Other bias	Unclear risk	Relevant information needed for assessment not provided

RV5 Ciarlet 2009-EU

Methods	RCT **Length of follow-up:** up to 42 days after last dose **Adverse event data collection methods:** see outcome measures; passive method used for reactogenicity, and active method used for serious adverse events
Participants	**Number:** 403 enrolled; 403 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants, aged 6 to 12 weeks; mothers negative for hepatitis B surface antigen; no known history of congenital abdominal disorders; intussusception, or abdominal surgery; no known or suspected impairment of immunological function; no

	history of seizure with or without fever; no known hypersensitivity to any component of rotavirus vaccine or INFANRIX hexa; no prior receipt of any rotavirus, DTaP, DTP, *H. influenzae* type b, Hepatitis B, injectable poliovirus vaccine, or oral polio vaccine during the course of the study, within 42 days before first dose of RV5 or before final blood draw (42 days after dose 3); no fever, with a rectal temperature < 38.1 °C (< 100.5 °F) at the time of immunization; no history of known rotavirus disease, chronic diarrhoea, or failure to thrive; no clinical evidence of active gastrointestinal illness; no prior receipt of intramuscular, oral, or intravenous corticosteroids treatment within 2 weeks before vaccination; did not reside in a household with an immunocompromised person; no receipt of a blood transfusion or blood products, including immunoglobulin; did not participate in another clinical study within 42 days before or during current study; could be adequately followed for safety **Exclusion criteria:** as above
Interventions	RV5 1. WC3 (RV5) plus Infanrix hexa: RV5 (2 mL; 3 doses given 4 to 6 weeks apart); 201 participants (randomized) 2. Placebo plus Infanrix hexa: placebo (2 mL; 3 doses given 4 to 6 weeks apart); 202 participants (randomized) **Infanrix hexa:** comes in 2 parts; first part is a white, milky liquid (0.5 mL) in a pre-filled syringe that consists of the combined diphtheria, tetanus, pertussis, hepatitis b, and inactivated poliovirus vaccine; second part is the *H. influenzae* type b vaccine and is a white pellet in a separate glass vial; both parts mixed together before being injected intramuscularly
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity: in both groups, at each study visit, parents/legal guardians received Vaccination Report Cards (VRCs) which they completed for 7 days with information regarding fever, diarrhoea, and vomiting starting from the day of office visit and returned completed VRCs to the study site at the next visit 2. Serious adverse events: parents/legal guardians of all participants were contacted by telephone or home visit on approximately day 14 after each office visit in either group for safety follow-up and asked about all serious adverse experiences; measured up to 42 days 3. All-cause death 4. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity** None specific to review
Immunization status	Hepatitis B vaccine, diphtheria-tetanus-acellular pertussis, polio virus, and *H. influenzae* type b co-administered
Location	26 study sites in Austria, Belgium, and Germany WHO mortality stratum A
Notes	**Date:** 22 February 2006 to 13 November 2006 **Source of funding:** Merck & Co., Inc. **Other:** only data about serious adverse events and adverse events leading to discontinuation are provided

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated randomized 1:1 to receive hexavalent vaccine concomitantly with either RV5 (RotaTeq) or placebo (Merck 2012)
Allocation concealment (selection bias)	Low risk	Allocation numbers were generated for participants, investigators, adults, and parents/guardians of children were blinded throughout trial (Merck 2012)
Blinding (performance bias and detection bias) All outcomes	Low risk	RV5 was visibly indistinguishable from placebo, investigators, parents/guardians and study personnel (internal and external) were blinded throughout trial (Merck 2012)
Incomplete outcome data (attrition bias) All outcomes	Low risk	"In both treatment groups (RV5+Hexavalent and Placebo+Hexavalent), 84% of the infants reported 1 or more adverse events within 14 days after vaccination. One subject discontinued in the concomitant-use group because of abdominal pain (considered non-serious)" (Merck 2012)
Selective reporting (reporting bias)	High risk	Not all pre-specified outcomes reported
Other bias	Unclear risk	No details

RV5 Clark 2003-USA

Methods	RCT **Length of follow-up:** up to 1 year **Adverse event data collection methods:** parents/guardians recorded temperatures 4 to 6 h after each dose and then daily thereafter for 7 days and the number of episodes of vomiting and diarrhoea daily for 7 days (passive method); also recorded any behavioral or systemic adverse experience on a vaccination report card and was asked to report any serious adverse experience immediately to the study site; telephone call made to each parent/guardian 14 days after each dose to verify that no serious adverse experiences had occurred (active)
Participants	**Number:** 731 enrolled; 681 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Special groups:** breast fed; infants in the vaccine control group (Group 1) received

	the reassortants as administered in previous studies within 30 min of feeding Enfamil formula (30 ml) or Mylanta Double Strength (0.5 ml/kg). Infants in a corresponding placebo group (Group 2) were pre-fed as in Group 1 **Inclusion criteria:** healthy infants 2 to 4 months of age **Exclusion criteria:** known hypersensitivity to any component of the rotavirus vaccine; known or suspected immunologic impairment; prior administration of any rotavirus vaccine; fever at the time of vaccination; history of chronic diarrhoea; failure to thrive or gastrointestinal illness; recent receipt of oral polio vaccine or blood products; residence in the household with an immunocompromised person; and failure to fast for 1 h before vaccination
Interventions	RV5 1. WC3 (RV5): 10^7 PFU; 581 participants (randomized) 2. Placebo: 581 participants (randomized) **Schedule:** 3 doses given 42 to 56 days apart
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity: parents/guardians recorded temperatures 4 to 6 h after each dose and then daily thereafter for 7 days and the number of episodes of vomiting and diarrhoea daily for 7 days; fever defined as 38.1°C (rectal) or 37.5°C (oral, otic, or axillary); measured up to 42 days after vaccine/placebo 2. Rotavirus diarrhoea: case of rotavirus gastroenteritis defined as ≥ 3 watery or looser than normal stools within a 24-h period and/or forceful vomiting occurring at least 14 days after the third dose of vaccine/placebo and detection by ELISA of wild-type G1 and/or G2 rotavirus in a stool specimen collected within 14 days of symptom onset; measured up to 1 year 3. Severe rotavirus diarrhoea: clinical scoring system used to assess severity of illness for each episode of rotavirus acute gastroenteritis; measured up to 1 year 4. Serious adverse events: defined as: death; life-threatening events; experiences that resulted in hospitalization, persistent disability, or that prolonged a hospitalization; and other important medical events. Data on deaths or any serious adverse experiences judged to be vaccine related were collected for the duration of the study; measured up to 1 year 5. Intussusception, data from correspondence with Merck (Merck 2012) 6. Drop outs **Outcomes to measure immunogenicity** 7. Viral shedding: at least a 3-fold rise in serum-neutralizing antibody to total stool IgA (review includes data from after dose 3) 8. Seroconversion: at least a 3-fold rise in serum-neutralizing antibody to serum IgA (review includes data from after dose 3)
Immunization status	Children that had recently received oral polio vaccine were excluded from the study
Location	19 centres in the USA WHO mortality stratum A
Notes	**Date:** September 1997 through September 1998 **Source of funding:** Merck & Co., Inc. **Other:** active surveillance for cases of rotavirus gastroenteritis at each study site began when the local laboratory confirmed at least 3 cases of rotavirus gastroenteritis or on 31

RV5 Clark 2003-USA (*Continued*)

	January 1998, whichever came first

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details; "Children who met all eligibility criteria were randomized to one of eight treatment groups"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and key personnel; "Parents of participating infants and study personnel were blinded to receipt of vaccine/placebo but not to the volume administered or to the prefeeding requirement"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions
Selective reporting (reporting bias)	High risk	Not all pre-specified outcomes reported; "Because there were relatively few confirmed cases of RV [rotavirus] caused by serotypes G1 and G2, the evidence is insufficient to declare that the efficacy of any buffered formulation is > 0.0%"
Other bias	High risk	Poor reporting of efficacy data

RV5 Clark 2004-USA

Methods	RCT **Length of follow-up:** up to 1 year (season) **Adverse event data collection methods:** episodes of fever (subjective assessment of fever) , vomiting, diarrhoea, behavioural changes, and any other adverse experiences during the 14 days after each dose also were reported on the diary card (passive method); parents were asked to report any serious adverse experience immediately to the study site (passive method); telephone call made to each participant 14 days after each vaccination to ask about serious adverse experiences (active method)
Participants	**Number:** 439 enrolled; 416 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants approximately 2 to 6 months of age were enrolled and followed for episodes of acute gastroenteritis **Exclusion criteria:** known hypersensitivity to any component of the rotavirus vaccine; known or suspected immunologic impairment; prior administration of any rotavirus vaccine; fever at time of vaccination (> 38.1 °C rectal); history of chronic diarrhoea or

	failure to thrive; clinical evidence of gastrointestinal illness; receipt of any other vaccines within 14 days; immunocompromised resident in the home; or any condition, which, in the opinion of the investigator, might interfere with the evaluation of the study objectives
Interventions	RV5 1. WC3 (RV5): 10^7 PFU; 3 doses at 6 to 8 week intervals; 218 participants (randomized) 2. Placebo: 3 doses at 6 to 8 week intervals; 221 participants (randomized)
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Rotavirus diarrhoea: case of rotavirus disease in a study participant defined as ≥ 3 watery or looser than normal stools within a 24-h period and/or forceful vomiting occurring at least 14 days after the third dose of vaccine/placebo and identification of rotavirus in a stool specimen obtained within 14 days of symptom onset; measured up to 1 year 2. Severe rotavirus diarrhoea: based on a clinical scoring system for evaluating the severity of an episode of infant acute gastroenteritis (0 to 24 points) they consider severe above 16 points; measured up to 1 year 3. Drop outs: measured up to 1 year 4. Serious adverse events: serious adverse experiences included death, life-threatening events, and experiences that resulted in hospitalization, persistent disability, or that prolonged a hospitalization; deaths or any serious adverse experiences judged to be vaccine-related were recorded for the duration of the study; measured up to 1 year, including intussusception (data from correspondence with Merck, Merck 2012). 5. Reactogenicity: all participants were followed for clinical adverse experiences for 14 days after each vaccination 6. Adverse events requiring discontinuation; measured up to 1 year **Outcomes to measure immunogenicity** 7. Viral shedding: stools were collected to evaluate vaccine strain shedding among subsets of infants at different time periods after each dose [review includes data from after dose 3] 8. Seroconversion: pre-vaccination and post-vaccination sera assayed for anti-rotavirus immunoglobulin A (IgA) and anti-rotavirus IgG (units/mL, based on pooled human serum standards); ≥ 3-fold rise in titre from baseline to after dose 3 (review includes data from after dose 3)
Immunization status	Receipt of any other vaccines within 14 days was not allowed
Location	10 study sites in the USA WHO mortality stratum A
Notes	**Date:** August 1993 to June 1994 **Source of funding:** Merck & Co., Inc.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

RV5 Clark 2004-USA (*Continued*)

Random sequence generation (selection bias)	Unclear risk	"Infants who met all eligibility criteria were randomly assigned in a 1:1 ratio". No further details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding (performance bias and detection bias) All outcomes	Low risk	"The vials of vaccine and placebo were visibly indistinguishable" "The placebo was identical to the vaccine except that it did not contain the rotavirus reassortants". Investigators, study personnel (internal and external), and parents/guardians were blinded throughout trial. (Merck 2012)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions
Selective reporting (reporting bias)	High risk	≥ 1 outcome of interest reported incompletely; "Only wild-type (ie, non-vaccine related) rotavirus cases were considered for the primary case definition"
Other bias	Unclear risk	Not enough detail to make a judgment

RV5 Kim 2008-KOR

Methods	RCT **Length of follow-up:** up to 42 days after last dose **Adverse event data collection methods:** diary cards (passive method)
Participants	**Number:** 178 enrolled; 171 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants; 6 to 12 weeks of age **Exclusion criteria:** history of congenital abdominal disorders, intussusception, or abdominal surgery; known or suspected impairment of immunological function; known hypersensitivity to any component of the rotavirus vaccine; prior receipt of any rotavirus vaccine; fever, with a rectal temperature ≥ 38.1 °C (≥ 100.5 °F) at the time of immunization; history of known prior rotavirus disease, chronic diarrhoea, or failure to thrive; clinical evidence of active gastrointestinal illness (infants with gastro-oesophageal reflux disease were permitted to participate in the study as long as the gastro-oesophageal reflux disease was well controlled with or without medication); receipt of intramuscular, oral, or intravenous corticosteroid treatment between the 2 weeks before first vaccination and 2 weeks after last vaccination; reside in a household with an immunocompromised person; prior receipt of a blood transfusion or blood products, including immunoglobulins; receipt of OPV during the course of the study or within 42 days before first dose of vaccine/placebo; and condition, which, in the opinion of the investigator, may have interfered with the evaluation of the study objectives

RV5 Kim 2008-KOR (*Continued*)

Interventions	RV5 1. WC3 (RV5): 6.9 to 8.6 x 10^7 PFU; 3 doses given 4 to 10 weeks apart; 115 participants (randomized) 2. Placebo: 3 doses given 4 to 10 weeks apart; 3 participants (randomized)
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Serious adverse events: no definition; measured up to 42 days 2. Reactogenicity: no definition; measured up to 14 days 3. Adverse events resulting in discontinuation **Outcomes to measure immunogenicity** 4. Seroconversion: seroresponse serum anti-rotavirus immunoglobulin A (IgA) defined as an increase in antibody titre by a factor of $\geq$ 3 from baseline (data could not be extracted for review)
Immunization status	Infants excluded if they had or were to receive oral poliovirus vaccine at any time during the study or in the 42 days before the first dose; concomitant administration of other licensed vaccines and breastfeeding was not restricted
Location	8 study centres in South Korea WHO mortality stratum B
Notes	**Date:** 2 August 2005 (first patient in) to 25 May 2006 (last dose given); last participant completed follow-up on 5 July 2006 **Source of funding:** Merck & Co., Inc. **Other:** most of the outcome data is not provided in the reports

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated randomized 2:1 to receive hexavalent vaccine concomitantly with either RV5 (RotaTeq) or placebo (Merck 2012)
Allocation concealment (selection bias)	Low risk	Allocation numbers were generated for participants, investigators, adults, and parents/guardians of children were blinded throughout trial (Merck 2012)
Blinding (performance bias and detection bias) All outcomes	Low risk	RV5 was visibly indistinguishable from placebo, investigators, study personnel (internal and external), and parents/guardians were blinded throughout trial (Merck 2012)
Incomplete outcome data (attrition bias) All outcomes	High risk	Reason related to outcome

Selective reporting (reporting bias)	High risk	Key expected outcome not included
Other bias	Unclear risk	Information not provided

RV5 Merck[009] 2005-USA

Methods	RCT **Length of follow-up:** up to 42 days after vaccination **Adverse event data collection methods:** not reported
Participants	**Number:** 793 enrolled; 706 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants; 6 to 12 weeks of age **Exclusion criteria:** history of congenital abdominal disorders, intussusception, or abdominal surgery; known or suspected impairment of immunological function; known hypersensitivity to any component of the rotavirus vaccine; prior receipt of any rotavirus vaccine; fever, with a rectal temperature ≥ 38.1 °C (≥ 100.5 °F) at the time of immunization; history of known prior rotavirus disease, chronic diarrhoea, or failure to thrive; clinical evidence of active gastrointestinal illness (infants with gastro-oesophageal reflux disease were permitted to participate in the study as long as the gastro-oesophageal reflux disease was well controlled with or without medication); receipt of intramuscular, oral, or intravenous corticosteroid treatment between the 2 weeks before first vaccination and 2 weeks after last vaccination; reside in a household with an immunocompromised person; prior receipt of a blood transfusion or blood products, including immunoglobulins; receipt of oral polio vaccine during the course of the study or within 42 days before first dose of vaccine/placebo; and condition, which, in the opinion of the investigator, may have interfered with the evaluation of the study objectives
Interventions	RV5 1. WC3 (RV5): 2 mL (10.7 PFU); 3 doses given at 4 to 10 week intervals; 680 participants (randomized) 2. Placebo: 3 doses given at 28 to 70 day intervals; 113 participants (randomized)
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Reactogenicity: no definition; measured 7 days after vaccination 2. Drop outs: measured up to 42 days 3. Adverse events requiring discontinuations: measured up to 42 days, (data from correspondence with Merck; Merck 2012). 4. Serious adverse events: not defined; measured up to 42 days, including intussusception (data from correspondence with Merck; Merck 2012). 5. Number of deaths (data from correspondence with Merck; Merck 2012). **Outcomes to measure immunogenicity** None
Immunization status	Infants were excluded if they had or were to receive oral poliovirus vaccine at any time during the study or in the 42 days before the first dose; concomitant administration of other licensed vaccines and breastfeeding was not reported

RV5 Merck[009] 2005-USA (*Continued*)

Location	10 centres in USA WHO mortality stratum A
Notes	**Date:** 9 May 2003 to 13 August 2004 **Source of funding:** Merck & Co., Inc. **Study objective:** "Comparison of the Immunogenicity and Safety of Three Consistency Lots of RotaTeq in Healthy Infants"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated randomization to 1 of 4 treatment groups. A randomization scheme of 2:2:2:1, with a blocking factor of 14, was used and subjects received either 1 of 3 lots of RV5 or placebo (Merck 2012)
Allocation concealment (selection bias)	Low risk	Allocation numbers were generated for participants, investigators, adults, and parents/guardians of children were blinded throughout trial (Merck 2012)
Blinding (performance bias and detection bias) All outcomes	Low risk	RV5 was visibly indistinguishable from placebo, investigators, study personnel (internal and external) and parents/guardians were blinded throughout trial (Merck 2012)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

RV5 NCT00718237 2010-JPN

Methods	RCT **Length of follow-up:** 25 months **Adverse event data collection methods:** any death, vaccine-related serious adverse events and intussusception were collected during the study period; parents/guardians asked to record adverse events on a standardized vaccine report card during 14 days after each vaccination
Participants	**Number:** 762 **Age range:** 6 to 12 weeks **Inclusion criteria:** healthy Japanese Infants

	Exclusion criteria: history of known prior rotavirus gastroenteritis; subjects who are concurrently participating in or are anticipated to participate in other studies of investigational products at any time during the study period
Interventions	1. Rotavirus vaccine, live, oral, pentavalent [RV5], 381 participants 2. Placebo (unspecified), 381 participants **Schedule:** 3 doses, 28 to 70 days apart, with 14 days of safety follow-up after each vaccination, and follow-up for acute gastroenteritis episodes until the end of the study
Outcomes	1. Efficacy against rotavirus gastroenteritis of any severity, at least 14 days following the 3rd vaccination 2. Efficacy against moderate to severe and severe rotavirus gastroenteritis, at least 14 days following the 3rd vaccination 3. Serious adverse events, including intussusception (data from correspondence with Merck; Merck 2012). 4. Reactogenicity (fever, vomiting, diarrhoea) 5. Drop-outs before the end of the trial 6. Adverse events leading to discontinuation of the trial 7. Number of deaths (data from correspondence with Merck; Merck 2012).
Immunization status	No information about other vaccines given
Location	32 sites in Japan WHO mortality stratum A
Notes	**Date:** August 2008 to September 2009 **Registration number:** NCT00718237 **Source of funding:** Merck Sharp & Dohme Corp **Rationale:** "to evaluate whether V260 is effective and well tolerated in Japanese healthy infants"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Allocation number was assigned and the subject was randomized to the group receiving RV5 or the group receiving placebo in a 1:1 ratio according to the randomization code prepared by a computer at the US Merck Headquarters Office" (Merck 2012)
Allocation concealment (selection bias)	Low risk	Allocation numbers were generated and allocated centrally for participants (Merck 2012)
Blinding (performance bias and detection bias) All outcomes	Low risk	RV5 was visibly indistinguishable from placebo, investigators, study personnel (internal and external) and parents/guardians

RV5 NCT00718237 2010-JPN (*Continued*)

		were blinded throughout trial (Merck 2012)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition/exclusions balanced across groups
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Sponsor: Merck

RV5 NCT00953056 2010-CHI

Methods	RCT **Length of follow-up:** two weeks after last dose **Adverse event data collection methods:** not reported
Participants	**Number:** Infant cohort: 48 enrolled and randomized **Inclusion criteria:** healthy infants aged 6 to 12 weeks **Exclusion criteria:** receiving other live vaccines 14 days before or after study vaccine; prior administration of any rotavirus vaccine; elevated temperature, with axillary temperature ≥ 37.1 °C 24-h before study vaccine; Prior or active gastrointestinal illnesses; immunodeficiency
Interventions	1. 2.0 mL doses of RV5 (V260) administered orally. The vaccine consists of an oral solution of 5 live human-bovine reassortant rotaviruses 2. 2.0 mL doses of matching placebo to RV5 administered orally **Schedule:** 3 doses of RV5/placebo at 3 separate visits scheduled 28 to 70 days apart. The third dose was administered by 32 weeks of age
Outcomes	**Clinical outcome measures** 1. Serious adverse events, up to 14 days post vaccination, including intussusception (data from correspondence with Merck; Merck 2012). 2. Adverse events requiring discontinuation 3. Drop outs from the trial 4. Number of deaths (data from correspondence with Merck; Merck 2012). **Outcomes to measure immunogenicity** 4. Vaccine virus shedding in stools, day 3 to day 7 following each of the 3 doses of RV5/placebo
Immunization status	Other live vaccines 14 days before or after study vaccine were not allowed
Location	China WHO mortality stratum B
Notes	**Date:** September 2009 to March 2010 **Source of funding:** Merck Sharp & Dohme Corp **Study rationale:** "This study will assess the safety and tolerability of RV5 (V260) in the healthy Chinese populations. Approximately 144 participants will be enrolled and

	equally stratified into three age cohorts, Cohort I ages 19-47 years, Cohort II ages 2-6 years, and Cohort III ages 6-12 weeks"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	All subjects were randomized according to a computer generated allocation schedule (Merck 2012)
Allocation concealment (selection bias)	Low risk	Allocation numbers were generated for participants, investigators, adults, and parents/guardians of children were blinded throughout trial (Merck 2012)
Blinding (performance bias and detection bias) All outcomes	Low risk	RV5 was visibly indistinguishable from placebo, investigators, study personnel (internal and external) and parents/guardians were blinded throughout trial (Merck 2012)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition balanced across groups with reasons reported for withdrawal
Selective reporting (reporting bias)	Unclear risk	Trial report does not provide enough information
Other bias	Unclear risk	Funded by Merck Sharp & Dohme Corp

RV5 Vesikari 2006a-FIN

Methods	RCT **Length of follow-up:** 1 to 3 rotavirus seasons (1 to 3 years) **Adverse event data collection methods:** diary cards (passive method); telephone calls to parents/legal guardians to ask about serious adverse events (active method) **Note:** the per-protocol population used for the primary efficacy analysis included 1496 participants after exclusion of 450 participants (23.1%). The modified intention-to-treat population used in a secondary efficacy analysis consisted of the 1647 participants, including protocol violators, who had any valid post-dose 3 efficacy data
Participants	**Number:** 1946 enrolled; 1496 evaluable (after 2 years) **Age range:** 3 to 6 months (beginning); > 6 months (end) **Inclusion criteria:** healthy infants between 2 and 8 months of age **Exclusion criteria:** not described
Interventions	RV5 1. WC3 (RV5)

	1.1. G1-4, P1A (2.69 x 10^7, 7.92 x 10^6, 2.41 x 10^6); 3 doses given 4 to 8 weeks apart; 1027 participants (randomized) 1.2. G1-4 (2.9 x 10^7); 3 doses given 4 to 8 weeks apart; 270 participants (randomized) 1.3. P1A (9.24 x 10^7); 3 doses given 4 to 8 weeks apart; 327 participants (randomized) 2. Placebo: 3 doses given 4 to 8 weeks apart; 322 participants (randomized) *We excluded the two arms dealing with different G or P serotypes and compared a single arm to placebo*
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Rotavirus diarrhoea: case definition for rotavirus gastroenteritis required: (1) ≥ 3 watery or looser-than-normal stools within a 24-h period and/or forceful vomiting; and (2) rotavirus antigen detection by EIA. The primary analysis of efficacy considered episodes as positive only when caused by wild-type rotavirus with a vaccine G serotype (G1, G2, G3, or G4) confirmed by polymerase chain reaction (PCR) occurring at least 14 days after the third dose of vaccine; measured 1 to 3 years 2. Severe rotavirus diarrhoea: clinical scoring system based on the intensity and duration of symptoms of fever, vomiting, diarrhoea, and behavioural changes was used to rate the severity of gastroenteritis, using a 24-point severity scale where a score of 1 to 8 was designated as mild, > 8 was designated as moderate-and-severe, and > 16 was designated as severe; measured 1 to 3 years 3. Reactogenicity: not defined other than all participants were followed for clinical adverse events for 42 days after each dose of vaccine or placebo; parents/guardians were provided with diary cards to record adverse events 4. Serious adverse events: not defined; noted that they were to be reported immediately. Parents/legal guardians were contacted by phone approximately 14 days after each dose and asked about serious adverse events. Data on deaths and serious adverse events judged by the investigator to be vaccine related were collected for the duration of the study (up to 42 days) 5. All-cause diarrhoea 6. All-cause diarrhoea - severe 7. All-cause death **Outcomes to measure immunogenicity** 8. Seroconversion: prevaccination and postvaccination sera assayed for rotavirus-specific IgA by ELISA with seroconversion defined as ≥ 3-fold rise in antibody titre from baseline to 2 weeks after dose 3 (review includes data from 14 days after dose 3)
Immunization status	Licensed vaccines could be administered throughout the study, but were not given on the same day as study vaccine; inactivated poliovirus vaccine was exclusively used in Finland at the time of the study
Location	4 sites (Tampere, Espoo, Lahti, Pori) in Finland WHO mortality stratum A
Notes	**Date:** June 1998 and June 2001 **Source of funding:** Merck & Co., Inc. **Other:** in total, 1946 infants (1300 in the first year and 646 in the second year of the study) were enrolled in the study and received at least the first dose of 1 of the 5 active vaccines or placebo. Overall, 1813 (93.2%) participants received 3 three doses and were followed for ≥ 42 days after the final dose. 1800 participants (92.5%) were

	followed through the first rotavirus season after vaccination; 1740 participants (89.4%) were followed through a second rotavirus season. Of the 1300 participants enrolled in the first year, 880 (67.7%) were followed through a third rotavirus season

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated (Merck 2012)
Allocation concealment (selection bias)	Low risk	Allocation numbers were generated for participants, investigators and parents/ guardians were blinded throughout trial (Merck 2012)
Blinding (performance bias and detection bias) All outcomes	Low risk	Sequential identical containers; "The vials containing either vaccine or placebo were visibly indistinguishable." Participants and key personnel; "This randomized clinical trial blinded to subject, investigator, parent/legal guardian, and sponsor. The placebo was identical to the vaccine except that it did not contain rotavirus reassortants or trace trypsin"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions
Selective reporting (reporting bias)	High risk	≥1 outcome of interest reported incompletely
Other bias	Unclear risk	Insufficient information to assess

RV5 Vesikari 2006b-INT

Methods	RCT **Length of follow-up:** up to 43 days for safety outcomes, and up to 2 years for efficacy outcomes **Adverse event data collection methods:** active surveillance was used to obtain safety data; parents or legal guardians were contacted on days 7, 14, and 42 after each dose and every 6 weeks thereafter for 1 year after the first dose with respect to intussusception and serious adverse events (active method)
Participants	**Number:** 70,301 enrolled and 69,274 randomized (efficacy study subpopulation of 5673); 57,134 evaluable for safety outcomes; for efficacy outcomes, 4512 evaluable in year 1 and 1569 evaluable in year 2 **Age range:** 1 to 3 months (beginning); 3 to 6 months (end)

	Inclusion criteria: healthy infants between 6 and 12 weeks of chronological age were eligible regardless of gestational age; no known history of congenital abdominal disorders, intussusception, or abdominal surgery; no known or suspected impairment of immunological function; no known hypersensitivity to any component of the rotavirus vaccine; no prior receipt of any rotavirus vaccine; no fever, with a rectal temperature ≥ 38.1 °C (≥ 100.5 °F) at the time of immunization; no history of known prior rotavirus disease, chronic diarrhoea, or failure to thrive; no clinical evidence of active gastrointestinal illness; no receipt of intramuscular, oral, or intravenous corticosteroid treatment within the 2 weeks before vaccination; did not reside in a household with an immunocompromised person; no prior receipt of a blood transfusion or blood products, including immunoglobulins; no receipt of oral poliovirus vaccine during the course of the study or within 42 days prior to the first dose of vaccine/placebo **Exclusion criteria:** see above for details **Special group:** infants born at < 36 weeks of gestational age were considered premature and infants born at < 32 weeks of gestational age were considered extremely premature; no formal safety or efficacy hypotheses were prespecified for premature infants
Interventions	RV5 1. WC3 (RV5): 2 mL (6.7 to 12.4 x 10^7 PFU); 3 doses given 4 to 10 weeks apart; 34,644 participants (randomized) 2. Placebo: 2 mL; 3 doses given 4 to 10 weeks apart; 34,630 participants (randomized)
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Rotavirus diarrhoea: case definition for rotavirus gastroenteritis required participants to meet both of the following criteria: (1) ≥ 3 watery or looser-than-normal stools within a 24-h period and/or forceful vomiting, and (2) rotavirus detected by EIA in a stool specimen taken within 14 days after the onset of symptoms. Only naturally occurring "rotavirus AGEs" caused by the composite of the human rotavirus G-serotypes in the vaccine (G1, G2, G3, and G4) occurring through the first rotavirus season that began at least 14 days following the third vaccination were included in the primary analysis; measured up to 2 years follow-up 2. Severe rotavirus diarrhoea: an established clinical scoring system based on the intensity and duration of fever, vomiting, diarrhoea, and changes in behaviour used to categorize episodes of rotavirus gastroenteritis on a 24-point severity scale; scores > 16 were considered to indicate severe disease; measured up to 2 years follow-up 3. Emergency department visit: hospitalizations and emergency department visits for acute gastroenteritis; measured up to 1 year of follow-up 4. All-cause hospital admission: see above; measured up to 1 year of follow-up 5. All-cause mortality: measured up to 1 year of follow-up 6. Drop outs: no definition; measured up to 2 years follow-up 7. Serious adverse events: monitored for at least 42 days after each dose for serious adverse events, including intussusception. All suspected cases of intussusception were reported to an independent, blinded adjudication committee, which included a paediatric surgeon, a paediatric radiologist, and a paediatrician with extensive experience in emergency medicine. The committee adjudicated potential cases of intussusception according to a prespecified case definition that required confirmation of the diagnosis by radiography or at surgery or autopsy; measured up to 1 year of follow-up. Final intussusception results taken from CDC report (CDC 2010). 8. Reactogenicity: not defined; measured up to 43 days after vaccine

	9. Adverse events requiring discontinuation: not defined; measured up to 1 year of follow-up 10. Rotavirus diarrhoea resulting in hospitalization **Outcomes to measure immunogenicity** 11. Seroconversion: defined as an increase in the antibody titre by a factor of ≥ 3 from baseline (review includes data from 14 days after dose 3)
Immunization status	Administration of other licensed childhood vaccines and breastfeeding were not restricted; for a subset of subjects in the USA (U.A. concomitant use cohort), Merck also provided the licensed paediatric vaccines that were administered concomitantly (same day) with RV5 or placebo, which included Comvax, Infanrix, Ipol, and Prevnar
Location	356 primary study sites in Belgium, Costa Rica, Finland, Germany, Guatemala, Italy, Jamaica, Mexico, Puerto Rico, Sweden, Taiwan, and the USA WHO mortality strata A, B, D
Notes	**Date:** 12 January 2001 to 6 October 2004 **Source of funding:** Merck & Co., Inc. **Other:** there is a full report on premature babies that will be data extracted separately

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated randomized 1:1 to receive either RV5 (RotaTeq) or placebo (Merck 2012)
Allocation concealment (selection bias)	Low risk	Allocation numbers were generated for participants, investigators and parents/ guardians were blinded throughout trial (Merck 2012)
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and key personnel; "Randomized, multicenter, double blinded (operated under in-house blinding procedures), placebo controlled, safety and efficacy trial. The placebo was an exact match minus the virus"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes reported
Other bias	Unclear risk	Difficult to judge, as some important information about randomization/allocation concealment are not provided

RV5 Zaman 2010-AS

Methods	RCT **Length of follow-up:** up to 43 days for safety outcomes, and up to 2 years for efficacy outcomes **Adverse event data collection methods:** active surveillance was used to obtain safety data; parents or legal guardians were contacted on the first 14 days after each dose and every month thereafter for 1 year after the first dose with respect to intussusception and serious adverse events (active method). "Serious adverse events were classified with the US regulatory definition, in line with ICH guidance, and identified by monthly query and parental reporting at any time or identification by study staff in hospitals or clinics. Intussusception at any time was assessed with an additional detailed protocol. All these events were monitored by an independent, unmasked, data and safety monitoring board that met about twice a year during the course of the investigation. The board also provided guidance about enrolment and severity scoring"
Participants	**Number:** 2119 enrolled; 2036 randomized, 2016 evaluable **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants aged 4 to 12 weeks. Breastfeeding was not restricted and there was no enrolment restrictions based on HIV status, although HIV testing was not done **Exclusion criteria**: see above
Interventions	RV5 1. WC3 (RV5): 2 mL (6.7 to 12.4 x 10^7 PFU); 3 doses given 4 weeks apart; 1,018 participants (randomized) 2. Placebo: 2 mL; 3 doses given 4 weeks apart; 1,018 participants (randomized) **Schedule:** 3 doses given at a 4 week interval
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Serious adverse events 2. Death due to serious adverse events 3. Rotavirus diarrhoea: case definition for rotavirus gastroenteritis required participants to meet both of the following criteria: (1) $\geq$ 3 watery or looser-than-normal stools within a 24-h period and/or forceful vomiting, and (2) rotavirus detected by EIA in a stool specimen taken within 14 days after the onset of symptoms 4. Severe rotavirus diarrhoea: an established clinical scoring system based on the intensity and duration of fever, vomiting, diarrhoea, and changes in behaviour used to categorize episodes of rotavirus gastroenteritis on a 20-point severity scale; scores > 11 were considered to indicate severe disease; measured up to 2 years follow-up 5. All-cause diarrhoea 6. All-cause diarrhoea - severe 7. Reactogenicity *: symptoms of rotavirus illness, including fever, diarrhoea, and vomiting; measured for 7 days after each dose (review includes data from for the end of follow-up) *Data on fever and vomiting are provided only on figure 2 and data could not be extracted reliably* **Outcomes to measure immunogenicity** 8. Seroconversion: serum rotavirus IgA responses (increases in level of serum rotavirus IgA $\geq$ 4 fold) (review includes data from after dose 2)

Immunization status	All children in the study received the standard EPI vaccines (including oral poliovirus vaccine) starting at 6 weeks of age
Location	Sites in rural Matlab (Bangladesh) and urban and peri-urban Nha Trang (Vietnam) WHO mortality strata B, D
Notes	This trial was conducted in Bangladesh and Vietnam, data reported separately per country can be found under RV5 Zaman 2010-BGD and RV5 Zaman 2010-VNM. **Date:** March 29, 2007 to March 31, 2009 **Source of funding:** funded by PATH (GAVI Alliance grant) and Merck

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Unique allocation numbers were designated at Merck as pentavalent rotavirus vaccine or placebo with computer generated block randomization, with block sizes of six"
Allocation concealment (selection bias)	Low risk	"Vaccine and placebo packages were then labelled with allocation numbers and provided to sites in identical presentations. Sites were instructed to assign allocation numbers to participants in sequential order as they were enrolled"
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and staff: "Participants were enrolled by study staff, who remained masked to treatment assignment throughout the trial" Researchers: "The statistician from Merck who analysed the data and the Merck and PATH protocol teams were masked to treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes reported
Other bias	Low risk	Funded by PATH (GAVI Alliance grant) and Merck. Protocol published a prior with ClinicalTrials.gov, number NCT00362648. The study was designed by scientists from Merck, with substantial input from PATH staff and site investiga-

RV5 Zaman 2010-AS (*Continued*)

		tors. Merck had direct oversight or participation in every stage of the study. Merck also participated in pharmacovigilance, organised and led the data and safety monitoring board meetings, and did the data analysis. Staff from PATH independently monitored study execution at sites and participated in pharmacovigilance, data analysis, and data and safety monitoring board meetings. All authors had full access to the data, and the corresponding author had final responsibility for the decision to submit for publication

RV5 Zaman 2010-BGD

Methods	RCT **Length of follow-up:** up to 43 days for safety outcomes, and up to 2 years for efficacy outcomes **Adverse event data collection methods:** active surveillance was used to obtain safety data; parents or legal guardians were contacted on the first 14 days after each dose and every month thereafter for 1 year after the first dose with respect to intussusception and serious adverse events (active method). "Serious adverse events were classified with the US regulatory definition, in line with ICH guidance, and identified by monthly query and parental reporting at any time or identification by study staff in hospitals or clinics. Intussusception at any time was assessed with an additional detailed protocol. All these events were monitored by an independent, unmasked, data and safety monitoring board that met about twice a year during the course of the investigation. The board also provided guidance about enrolment and severity scoring"
Participants	**Number:** 1136 randomized **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants aged 4 to 12 weeks. Breastfeeding was not restricted and there was no enrolment restrictions based on HIV status, although HIV testing was not done **Exclusion criteria**: see above
Interventions	RV5 1. WC3 (RV5): 2 mL (6.7 to 12.4 x 10^7 PFU); 3 doses given 4 weeks apart; 568 (randomized) 2. Placebo: 2 mL; 3 doses given 4 weeks apart; 568 participants (randomized) **Schedule:** 3 doses given at a 4-week interval
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Serious adverse events 2. Death due to serious adverse events 3. Rotavirus diarrhoea: case definition for rotavirus gastroenteritis required participants to meet both of the following criteria: (1) $\geq$ 3 watery or looser-than-normal stools within a 24-h period and/or forceful vomiting, and (2) rotavirus detected by EIA in a stool

	specimen taken within 14 days after the onset of symptoms 4. Severe rotavirus diarrhoea: an established clinical scoring system based on the intensity and duration of fever, vomiting, diarrhoea, and changes in behaviour used to categorize episodes of rotavirus gastroenteritis on a 20-point severity scale; scores > 11 were considered to indicate severe disease; measured up to 2 years follow-up 5. All-cause diarrhoea 6. All-cause diarrhoea - severe 7. Reactogenicity *: symptoms of rotavirus illness, including fever, diarrhoea, and vomiting; measured for 7 days after each dose [review includes data from for the end of follow-up] *Data on fever and vomiting are provided only on figure 2 and data could not be extracted reliably* **Outcomes to measure immunogenicity** 8. Seroconversion: serum rotavirus IgA responses (increases in level of serum rotavirus IgA ≥ 4 fold) [review includes data from after dose 2]
Immunization status	All children in the study received the standard EPI vaccines (including oral poliovirus vaccine) starting at 6 weeks of age
Location	Sites in rural Matlab, Bangladesh WHO mortality stratum D
Notes	This trial was conducted in Bangladesh and Vietnam, this part presents data for the Bangladesh cohort, data reported separately for Vietnam can be found under RV5 Zaman 2010-VNM and data for both countries under RV5 Zaman 2010-AS **Date:** March 29, 2007 to March 31, 2009 **Source of funding:** funded by PATH (GAVI Alliance grant) and Merck

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Unique allocation numbers were designated at Merck as pentavalent rotavirus vaccine or placebo with computer generated block randomization, with block sizes of six"
Allocation concealment (selection bias)	Low risk	"Vaccine and placebo packages were then labelled with allocation numbers and provided to sites in identical presentations. Sites were instructed to assign allocation numbers to participants in sequential order as they were enrolled"
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and staff: "Participants were enrolled by study staff, who remained masked to treatment assignment throughout the trial"

RV5 Zaman 2010-BGD (*Continued*)

		Researchers: "The statistician from Merck who analysed the data and the Merck and PATH protocol teams were masked to treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes reported
Other bias	Low risk	Funded by PATH (GAVI Alliance grant) and Merck. Protocol published a prior with ClinicalTrials.gov, number NCT00362648. The study was designed by scientists from Merck, with substantial input from PATH staff and site investigators. Merck had direct oversight or participation in every stage of the study. Merck also participated in pharmacovigilance, organised and led the data and safety monitoring board meetings, and did the data analysis. Staff from PATH independently monitored study execution at sites and participated in pharmacovigilance, data analysis, and data and safety monitoring board meetings. All authors had full access to the data, and the corresponding author had final responsibility for the decision to submit for publication

RV5 Zaman 2010-VNM

Methods	RCT **Length of follow-up:** up to 43 days for safety outcomes, and up to 2 years for efficacy outcomes **Adverse event data collection methods:** active surveillance was used to obtain safety data; parents or legal guardians were contacted on the first 14 days after each dose and every month thereafter for 1 year after the first dose with respect to intussusception and serious adverse events (active method). "Serious adverse events were classified with the US regulatory definition, in line with ICH guidance, and identified by monthly query and parental reporting at any time or identification by study staff in hospitals or clinics. Intussusception at any time was assessed with an additional detailed protocol. All these events were monitored by an independent, unmasked, data and safety monitoring board that met about twice a year during the course of the investigation. The board also provided guidance about enrolment and severity scoring"
Participants	**Number:** 900 randomized **Age range:** 1 to 3 months (beginning); 3 to 6 months (end) **Inclusion criteria:** healthy infants aged 4 to 12 weeks. Breastfeeding was not restricted

	and there was no enrolment restrictions based on HIV status, although HIV testing was not done **Exclusion criteria**: see above
Interventions	RV5 1. WC3 (RV5): 2 mL (6.7 to 12.4 x 10^7 PFU); 3 doses given 4 weeks apart; 450 participants (randomized) 2. Placebo: 2 mL; 3 doses given 4 weeks apart; 450 participants (randomized) **Schedule:** 3 doses given at a 4 week interval
Outcomes	**Clinical outcome measures (safety and efficacy)** 1. Serious adverse events 2. Death due to serious adverse events 3. Rotavirus diarrhoea: case definition for rotavirus gastroenteritis required participants to meet both of the following criteria: (1) ≥ 3 watery or looser-than-normal stools within a 24-h period and/or forceful vomiting, and (2) rotavirus detected by EIA in a stool specimen taken within 14 days after the onset of symptoms 4. Severe rotavirus diarrhoea: an established clinical scoring system based on the intensity and duration of fever, vomiting, diarrhoea, and changes in behaviour used to categorize episodes of rotavirus gastroenteritis on a 20-point severity scale; scores > 11 were considered to indicate severe disease; measured up to 2 years follow-up 5. All-cause diarrhoea 6. All-cause diarrhoea - severe 7. Reactogenicity*: symptoms of rotavirus illness, including fever, diarrhoea, and vomiting; measured for 7 days after each dose [review includes data from for the end of follow-up] *Data on fever and vomiting are provided only on figure 2 and data could not be extracted reliably.* **Outcomes to measure immunogenicity** 8. Seroconversion: serum rotavirus IgA responses (increases in level of serum rotavirus IgA ≥ 4 fold) [review includes data from after dose 2]
Immunization status	All children in the study received the standard EPI vaccines (including oral poliovirus vaccine) starting at 6 weeks of age
Location	Sites in urban and peri-urban Nha Trang, Vietnam WHO mortality stratum B
Notes	This trial was conducted in Bangladesh and Vietnam, this part presents data for the Vietnam cohort, data reported separately for Bangladesh can be found under RV5 Zaman 2010-BGD and data for both countries under RV5 Zaman 2010-AS **Date:** March 29, 2007 to March 31, 2009 **Source of funding:** funded by PATH (GAVI Alliance grant) and Merck

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

RV5 Zaman 2010-VNM (*Continued*)

Random sequence generation (selection bias)	Low risk	"Unique allocation numbers were designated at Merck as pentavalent rotavirus vaccine or placebo with computer generated block randomization, with block sizes of six"
Allocation concealment (selection bias)	Low risk	"Vaccine and placebo packages were then labelled with allocation numbers and provided to sites in identical presentations. Sites were instructed to assign allocation numbers to participants in sequential order as they were enrolled"
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and staff: "Participants were enrolled by study staff, who remained masked to treatment assignment throughout the trial" Researchers: "The statistician from Merck who analysed the data and the Merck and PATH protocol teams were masked to treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced across groups
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes reported
Other bias	Low risk	Funded by PATH (GAVI Alliance grant) and Merck. Protocol published a prior with ClinicalTrials.gov, number NCT00362648. The study was designed by scientists from Merck, with substantial input from PATH staff and site investigators. Merck had direct oversight or participation in every stage of the study. Merck also participated in pharmacovigilance, organised and led the data and safety monitoring board meetings, and did the data analysis. Staff from PATH independently monitored study execution at sites and participated in pharmacovigilance, data analysis, and data and safety monitoring board meetings. All authors had full access to the data, and the corresponding author had final responsibility for the decision to submit for publication

RCT = Randomized controlled trial; ELISA = Enzyme Linked Immunosorbent Assay.

Immunogenicity: only data for review relevant outcomes listed in these tables.
MedDRA: Medical Dictionary for Regulatory Activities.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
OTHER Bucher 2012	Diagnostic test accuracy study
OTHER Chatterjee 2012	RCT, not rotavirus vaccine
OTHER Davidson 2007	Review article about RV5 and RV1
OTHER de Palma 2010	Case-control study
OTHER Diness 2010	Study of vitamin A supplementation with Bacille Calmette-Guerin vaccine for rotavirus diarrhoea outcomes
OTHER Dutta 2011	RCT, not rotavirus vaccine
OTHER Freedman 2007	Review article about acute infectious pediatric gastroenteritis
OTHER Gagneur 2011	Observational study (IVANHOE)
OTHER Glass 2004	Review article about rotavirus vaccines
OTHER Kapikian 1989	Review article about rotavirus vaccines
OTHER Kempe 2007	Survey of paediatricians about rotavirus disease and rotavirus vaccines
OTHER Muhsen 2010	Case-control study
OTHER NCT01195844	Ongoing observational study
OTHER NCT01236066	Ongoing observational study
OTHER NCT01375907	Ongoing study with adult participants
OTHER Prymula 2009	Review article about febrile reactions and vaccination
OTHER Rivera 2011	RCT, no placebo comparison
OTHER Tate 2012	Meta-analysis
OTHER Thyagarajan 2011	Procedural codes for rotavirus vaccination in the US
RV1 Anonymous 2004	Review article of the RV1 vaccine

(*Continued*)

RV1 Araujo 2007	Partial report of the Brazilian population in an included RV1 trial (RV1 Salinas 2005-LA)
RV1 Cervantes 2006	Letter to the Editor about RV1 trials
RV1 Cheuvart 2009	Review article of the RV1 vaccine
RV1 Correia 2010	Case-control study
RV1 CTRI/2012/02/002454	Ongoing RCT with no placebo group
RV1 De Vos 2006	Review article of the RV1 vaccine
RV1 De Vos 2009	Review article of the RV1 vaccine
RV1 Dennehy 2008	RCT of RV1 vaccine, but no placebo group reported
RV1 GSK[107077-057] 2008	RCT of RV1 vaccine, but no placebo group reported
RV1 GSK[107876-061] 2008	RCT of RV1 vaccine, but no placebo group reported
RV1 GSK[444563-020] 2007	RCT, but excluded because report mentioned that "4 groups received an investigational vaccination regimen", but no details are provided about this vaccine (may be related to GlaxoSmithKline's RV1 vaccine)
RV1 NCT00353366	Ongoing non-randomized study
RV1 NCT00382772 2008	RCT comparing RV1 liquid formulation to lyophilized formulation, no placebo
RV1 NCT00653198	Ongoing case-control study
RV1 NCT00655187	Ongoing case-control study
RV1 NCT01162590	Ongoing study with adult participants
RV1 NCT01177826	Ongoing observational study
RV1 NCT01273077	Ongoing observational study
RV1 NCT01339221	Ongoing observational study
RV1 PLOSKER 2011	Economic analysis
RV1 Rojas 2007	Viral conversion on the same population of RV1 Ruiz-Palac 06-LA/EU (included trial)
RV1 Suryakiran 2011	Not RCT, integrated safety summary
RV1 Vesikari 2006	Review article about RV1

(*Continued*)

RV5 [NCT00130832] 2010	Not RCT; open label study investigating different schedules of rotavirus and polio vaccine combinations without placebo
RV5 ACTRN12611000559910	Ongoing observational study
RV5 Bernstein 2008	Letter questioning the level of efficacy of RV5
RV5 Caple 2006	Review article about RV5
RV5 Ciarlet 2008	RCT of RV5 vaccine, but no placebo group reported
RV5 Clark 2006	Review article about RV5
RV5 El Khoury 2011	Mathematical model in Brazil
RV5 El Khoury 2011a	Mathematical model in six Asian countries
RV5 Goveia 2008	Retrospective analysis to check percentage of babies that were breastfeeding while participating in RV5 Vesikari 2006b-INT (included trial)
RV5 Goveia 2010	Post-hoc analysis of the Merck RV5 trials (mainly REST)
RV5 Heyse 2008	Review article about RV5
RV5 Keating 2006	Review article about RV5
RV5 NCT00496054	Ongoing non-randomized study
RV5 Tom-Revzon 2007	Review article about RV5
RV5 Tugcu 2009	RCT of RV5 vaccine, no placebo group reported
RV5 van der Wielen 2008	Review article about RV5
RV5 Vesikari 2011	RCT of RV5 and MenCC vaccines - concomitant or sequential administration, no placebo group reported

Characteristics of ongoing studies *[ordered by study ID]*

Other ACTRN12610000525088

Trial name or title	"A Phase 1 double-blind, randomized study to compare the safety, tolerability and immunogenicity of oral RV3-BB rotavirus vaccine and placebo in infants, children and male adults"
Methods	"Randomized controlled trial, parallel assignment"

Other ACTRN12610000525088 (*Continued*)

Participants	**Number:** 60 (target) **Description:** cohort 3: infants (males and females) aged 6 to 8 weeks inclusive in good health
Interventions	1 mL oral dose administered once 1. live attenuated human rotavirus vaccine RV3-BB 2. Placebo
Outcomes	1. Adverse events 2. Serologic markers of rotavirus immunity (immunoglobulin G (IgG) and immunoglobulin A (IgA), neutralising antibodies (NA's)) 3. Presence of RV3-BB rotavirus vaccine in faecal extracts
Starting date	27 January 2010 **Completion:** not stated
Contact information	Dr Carl Kirkwood, Murdoch Childrens Research Institute 4th Floor, Front Entry Building Royal Children's Hospital Flemington Road Parkville, Victoria 3052, Australia carl.kirkwood@mcri.edu.au
Notes	**Location:** Australia **Registration number:** ACTRN12610000525088 (Australian New Zealand Clinical Trials Registry) **Source of funding:** Murdoch Childrens Research Institute

Other ACTRN12611001212943

Trial name or title	A Phase IIa double-blind, randomized, placebo controlled study of the immunogenicity, safety, tolerability and reactogenicity of three doses of oral RV3-BB rotavirus vaccine, with the first dose of vaccine administered either at birth (0 to 5 days of age) or in infancy
Methods	Randomized, parallel assignment, blinded
Participants	**Number:** 93 (target) **Description:** healthy, full-term infants, 0 to 5 days of age
Interventions	1. Neonatal schedule arm: RV3-BB rotavirus vaccine at 0 to 5 days, 9 weeks, and 15 weeks of age + placebo at 23 weeks of age 2. Infant schedule arm: RV3-BB rotavirus vaccine at 9 weeks, 15 weeks, and 23 weeks of age + placebo at 0 to 5 days of age 3. Placebo
Outcomes	1. Vaccine shedding in stool 2. Solicited adverse events 3. Serious adverse events
Starting date	December 2011
Contact information	Professor Julie Bines; jebines@unimelb.edu.au

Other ACTRN12611001212943 (*Continued*)

Notes	**Location:** New Zealand **Registration number:** ACTRN12611001212943 **Source of funding:** Australian National Health and Medical Research Council; Australian Health Research Council; Murdoch Children's Research Institute

Other CTRI-091-000102

Trial name or title	"A Phase III, Randomized, Double blind, Placebo Controlled Trial to Evaluate the protective efficacy of three doses of Oral Rotavirus Vaccine (ORV) 116E, against severe Rotavirus gastroenteritis in infants "
Methods	"Randomized, Parallel Group, Placebo Controlled, Double-Blind Trial"
Participants	**Number:** 6800 (target) **Description:** infants aged 6 to 7 weeks at recruitment
Interventions	3 doses of 0.5 mL at 4 week intervals 1. Oral rotavirus vaccine 116E (ORV 116E) 2. Placebo
Outcomes	1. Severe rotavirus gastroenteritis (>/= 11 on the 20 point Vesikari scoring scale) 2. Any severity of gastroenteritis caused by non vaccine rotavirus 3. Any severity of gastroenteritis irrespective of etiology 4. Severe (>/= 11 on the 20 point Vesikari scoring scale) gastroenteritis irrespective of etiology 5. Hospitalization and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a treatment facility/hospital for gastroenteritis 6. Very severe rotavirus gastroenteritis (>/= 16 on the 20-point Vesikari scoring system)
Starting date	1 February 2011 **Completion:** not stated
Contact information	Dr. G.V.J.A. Harshavardhan, Bharat Biotech International Limited, Genome valley, Shameerpet 500078 Hyderabad, ANDHRA PRADESH, India, kmohan@bharatbiotech.com
Notes	**Location:** India **Registration number:** Clinical Trials Registry-India (CTRI/2010/091/000102) **Source of funding:** 1) Department of Biotechnology (DBT), Ministry of Science and Technology, Government of India CGO Complex, Lodhi Road, New Delhi, India 2) Bharat Biotech International Limited (BBIL), Genome Valley, Shameerpet, Hyderabad, Andhra Pradesh, India 3) PATH, 2201 Westlake Avenue, Suite 200, Seattle, WA 98121, USA & A-9, Qutab Institutional Area, New Delhi, India

Other CTRI-091-003064

Trial name or title	"A Randomized, Double-Blind, Placebo Controlled Study to Assess Safety and Tolerability of RotaVac Vaccine (Live Attenuated Bovine-Human (UK) Reassortant Pentavalent Rotavirus Vaccine)"
Methods	"Randomized, Parallel Group assignment, Placebo Controlled, Double-Blind Study"

Other CTRI-091-003064 (*Continued*)

Participants	**Number:** 60 (target) **Description:** healthy male or female infants 8-10 weeks of age at the time of first dose of vaccination
Interventions	3 Oral doses with 28 days interval between each dose 1. Rotavirus vaccine 2. Placebo
Outcomes	1. Unsolicited and serious adverse events 2. Solicited symptom within 14 day 3. Rotavirus-specific IgA antibody titre 4. Viral Shedding
Starting date	10 January 2011 **Completion:** not stated
Contact information	Dr. Sajjad Desai, Serum Institute of India Ltd, 212/2 Off Soli Poonawalla road, Hadapsar, 411028 Pune, MAHARASHTRA India, sajjad.desai@seruminstitute.com
Notes	**Location:** India **Registration number:** Clinical Trials Registry-India (CTRI/2010/091/003064) **Source of funding:** Serum Institute of India Ltd.

Other CTRI2009-091-000821

Trial name or title	"A Randomized, Double-Blind, Placebo Controlled Study To Assess the Safety And Tolerability Of RotaVac Vaccine (Live Attenuated Bovine-Human (UK) Reassortant Pentavalent Rotavirus Vaccine)"
Methods	"Randomized, parallel group, placebo controlled trial"
Participants	**Number:** not stated **Description:** healthy adults (aged between 18 and 45 years); healthy toddlers; and healthy infants
Interventions	RotaVac 1. RotaVac vaccine (live attenuated bovine-human (UK) reassortant pentavalent rotavirus vaccine): "Single oral dose in Part I of the study and three doses in Part II of the study" 2. Placebo: "Schedule matching with Rotavirus vaccine"
Outcomes	1. "Occurrence of any solicited symptom within 7-day solicited follow-up period" (Primary outcome) 2. "Occurrence of unsolicited and serious adverse events within 7 days after vaccination" (Primary outcome) 3. "Rotavirus-specific IgA antibody titre" (Secondary outcome) 4. "Presence of rotavirus antigen in any diarrhoeal stools during the 7-day solicited follow-up period" (Secondary outcome)
Starting date	21 October 2009 **Completion:** not stated
Contact information	Dr Anand Pandit, KEM Hospital, Pune, Maharashtra, India

Other CTRI2009-091-000821 (*Continued*)

Notes	**Location:** KEM Hospital, Pune, Maharashtra, India **Registration number:** Clinical Trials Registry India (CTRI/2009/091/000821, 15-10-2009); temporary unique trial identification number (UTRI) (104944555-0610200913021785) **Source of funding:** Serum Institute of India, Pune, India

Other NCT00981669

Trial name or title	"Evaluation of Rotavirus Vaccine Produced by Butantan Institute. Phase I - Safety, Tolerability and Immunogenicity Evaluation"
Methods	"Randomized, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Placebo Control, Parallel Assignment, Safety Study"
Participants	**Target number:** 80 **Description:** healthy males aged 18 to 40 years
Interventions	"An agreement between Path Foundation and Butantan Institute has made possible the transfer of technology to Butantan Institute to produce, at a reduced cost, a pentavalent rotavirus vaccine including the rotavirus serotypes more frequent in Brazil" 1. Rotavirus vaccine (3 doses with 6 weeks interval); other name: Brazilian rotavirus vaccine 2. Placebo (3 doses with 6 weeks interval); other name: Butantan placebo
Outcomes	"Titers of anti-rotavirus IgA and the presence of neutralizing antibodies anti-rotavirus"
Starting date	March 2009 **Anticipated completion date:** March 2010 [primary outcome], still ongoing
Contact information	Alexander R Precioso (Study Director), Butantan Institute, Brazil
Notes	**Location:** Brazil **Registration number:** NCT00981669 **Source of funding:** Butantan Institute, Brazil

Other NCT01061658

Trial name or title	"Phase I/II, Randomized, Double-blind, Placebo-controlled, Dosage Selection (10e5.5 or 10e6.25 FFU of Each Constituent Serotype Per 0.5 mL) Study to Evaluate the Safety, Tolerability, and Immunogenicity of a 3-dose Series of Live Attenuated Tetravalent (G1-G4) Bovine-Human Reassortant Rotavirus Vaccine [BRV-TV] Administered to Healthy Indian Infants"
Methods	"Randomized, Placebo Control, Safety Study, Parallel Assignment, Double Blind (Subject, Caregiver, Investigator)"
Participants	**Number:** 90 (target) **Description:** healthy infants 6 to 8 weeks of age at time of enrolment of either sex

Other NCT01061658 (*Continued*)

Interventions	1. Live attenuated tetravalent (G1-G4) bovine-human reassortant rotavirus vaccine 2. Placebo
Outcomes	1. Reactogenicity 2. Adverse events 3. Shedding of vaccine rotavirus in stool samples 4. Seroconversion rate 5. Sero-response rate 6. GMT of serum IgA antibody against rotavirus
Starting date	1 July 2010 **Completion:** not stated
Contact information	Gagandeep Kang, MD PhD, gkang@cmcvellore.ac.in
Notes	**Location:** India **Registration number:** NCT01061658 (http://clinicaltrials.gov) **Source of funding:** Shantha Biotechnics Limited

Other NCT01266850

Trial name or title	"Safety and Immunogenicity of Sequential Rotavirus Vaccine Schedules With RotaTeq® and Rotarix®"
Methods	"Randomized, Efficacy Study, Parallel Assignment, Open Label"
Participants	**Number:** 1266 (target) **Description:** male or female infants who are at least 6 weeks of age and no more than 14 weeks
Interventions	1. RV1 2. RV5
Outcomes	1. Geometric mean titer (GMT) serum anti-rotavirus immunoglobulin (Ig)A 2. Seroresponse rate 3. Comparison of systemic reaction incidences 4. GMT of neutralizing rotavirus antibody to the most common rotavirus serotypes (G1-G4 and G9)
Starting date	March 2011 **Estimated completion:** June 2013
Contact information	Kathryn M Edwards, kathryn.edwards@vanderbilt.edu
Notes	**Location:** US **Registration number:** NCT01266850 (http://clinicaltrials.gov) **Source of funding:** National Institute of Allergy and Infectious Diseases (NIAID)

Other NCT01305109

Trial name or title	"A Phase III, Randomized, Double Blind, Placebo Controlled Trial to Evaluate the Protective Efficacy of Three Doses of Oral Rotavirus Vaccine (ORV) 116E, Against Severe Rotavirus Gastroenteritis in Infants"
Methods	"randomized, placebo control, efficacy study, parallel assignment, double blind"
Participants	**Number:** 6800 (target) **Description:** infants aged 6 to 7 weeks at recruitment
Interventions	1. ORV 116E 2. Placebo
Outcomes	1. Severe rotavirus gastroenteritis (>= 11 on the 20 point Vesikari scoring scale) 2. Adverse events
Starting date	March 2011 **Estimated completion:** April 2014
Contact information	Dr. Nita Bhandari, MD, PhD, nita.bhandari@sas.org.in
Notes	**Location:** India **Registration number:** NCT01305109 (http://clinicaltrials.gov) **Source of funding:** Bharat Biotech International Limited

Other NCT01571505

Trial name or title	Exploration of the biologic basis for underperformance of oral polio and rotavirus vaccines in India (PROVIDE)
Methods	Randomized, efficacy study, parallel assignment, single blind
Participants	**Number:** 372 **Description:** healthy infants 0 to 49 days old with no obvious congenital abnormalities or birth defects
Interventions	1. Rotavirus vaccine (unspecified) with OPV + IPV booster 2. Rotavirus vaccine (unspecified) with OPV + OPV booster
Outcomes	1. Systemic immune responses 2. Mucosal immune responses
Starting date	March 2012 **Estimated completion:** February 2015
Contact information	Dipika Sur, M.D.; dipikasur@hotmail.com
Notes	**Location:** India **Registration number:** NCT01571505, CTRI/2012/03/002504 **Source of funding:** International Vaccine Institute

RV1 ISRCTN37373664

Trial name or title	"A double blind, randomized placebo controlled study of the safety, reactogenicity and immunogenicity of two doses of orally administered human rotavirus vaccine (RIX4414) in healthy infants in South Africa"
Methods	"A double blind, randomized placebo controlled study"
Participants	**Target number:** 285 **Description:** healthy infants aged 6 to 10 weeks
Interventions	1. RV1: 2 doses at $10^{6.5}$ CCID50 viral concentration 2. Placebo
Outcomes	1. Seroconversion 2. Immunogenicity: vaccine take; serum rotavirus immunoglobulin A (IgA) antibody concentrations; anti-poliovirus antibody titres; viral shedding 3. Safety: solicited symptom; unsolicited adverse events; presence of rotavirus in diarrhoeal stool; serious adverse events 4. Efficacy: rotavirus gastroenteritis/severe rotavirus gastroenteritis; severe rotavirus gastroenteritis
Starting date	1 January 2002 **Anticipated end date:** 25 October 2004, completed
Contact information	Dr Duncan Steele (steeled@who.int), WHO
Notes	**Location:** South Africa **Registration number:** ISRCTN37373664 **Source of funding:** RAPID trials (USA); WHO (Switzerland)

RV1 ISRCTN86632774

Trial name or title	"A phase II, double blind randomized, placebo controlled study to assess the safety reactogenicity and immunogenicity of three doses of GSK Biologicals (South Africa)"
Methods	"randomized, controlled study with three parallel groups with balanced allocation (1:1:1)"
Participants	Target number: 271 **Description:** participants' parents/guardians who could comply with the protocol requirements (eg completion of diary cards, return for follow-up visits); male or female aged 6 to 10 weeks of age at the time of first vaccination; written informed consent from parents/guardians; born after a gestation period of 36 to 42 weeks
Interventions	1. RIX4414 (RV1): 2 doses vaccine at $10^{6.5}$ CCID50 viral concentration plus 1 dose of placebo 2. Placebo: 3 doses
Outcomes	1. Seroprotection for each polio serotype (primary) 2. Vaccine take 3. Viral shedding 4. Presence of rotavirus in diarrhoeal stools 5. Anti-poliovirus antibody titres 6. Serum anti-rotavirus immunoglobulin A (IgA) antibody titres

RV1 ISRCTN86632774 (*Continued*)

	7. Solicited symptoms 8. Unsolicited adverse events 9. Serious adverse events
Starting date	1 January 2001 **Anticipated end date:** 1 January 2003, completed
Contact information	Dr Duncan Steele (steeled@who.int), WHO
Notes	**Location:** South Africa **Registration number:** ISRCTN86632774 **Source of funding:** RAPID trials (USA); WHO (Switzerland)

RV1 NCT00134732

Trial name or title	"Assess the Immunogenicity, Safety & Reactogenicity of 2 Doses of GSK Biologicals' Oral Live Attenuated Human Rotavirus (HRV) Vaccine in Healthy Infants (6-12 Weeks of Age at First Dose) Previously Uninfected With Human Rotavirus"
Methods	"Prevention, Randomized, Double-Blind, Parallel Assignment, Safety Study"
Participants	**Target number:** 150 **Description:** healthy infants aged between 6 and 12 weeks (42 to 90 days) of age at the time of the first vaccination
Interventions	1. Human rotavirus vaccine [RV1] 2. Placebo Both administered starting at 2 months of age according to a two dose schedule (0, 2 months)
Outcomes	1. Percent who seroconverted (anti-rota serum IgA, 2 months post dose 2) (primary) 2. Grade 2 and 3 fever, vomiting, diarrhoea, solicited symptoms 3. Unsolicited events 4. Serious adverse events 5. Presence of rotavirus in gastroenteritis 6. Concentration IgA 2 months post dose 2
Starting date	July 2005 **Completion date:** not stated, completed
Contact information	GSK Clinical Trials, GlaxoSmithKline
Notes	**Location:** Republic of Korea **Registration number:** NCT00134732 **Source of funding:** GlaxoSmithKline

RV1 NCT00158756

Trial name or title	"Assess Immunogenicity & Reactogenicity of 2 Formulations of GSK's DTPw-HBV Vaccines vs Concomitant Admn of CSL's DTPw [diphtheria-tetanus-pertussis] & GSK's HBV [Hepatitis B] Vaccine, co-Admnd With GSK's Rotavirus Vaccine, to Infants at 3, 4½ & 6 Mths, After Birth Dose of HBV Vaccine"
Methods	"Prevention, Randomized, Open Label, Active Control, Parallel Assignment"
Participants	**Number:** 330 **Description:** healthy infants aged 11 to 17 weeks of age at the time of the first DTPw vaccination
Interventions	5 groups 1. RV1 plus DTPw-HBVs 2 to 5. One of the two formulations of GSK Biologicals' DTPw-HBV + Placebo CSL's DTPw + GSK Biologicals' HBV
Outcomes	1. Anti-diphtheria antibody concentration (primary) 2. Antibody concentrations or titres against all vaccine antigens (diphtheria, tetanus, pertussis, hepatitis B, rotavirus, and poliovirus antigens) 3. Reactogenicity and safety: solicited symptoms; unsolicited symptoms; serious adverse events
Starting date	September 2005 **Anticipated completion date:** November 2006, completed
Contact information	Clinical Trials, GlaxoSmithKline
Notes	**Location:** Moscow, Russian Federation **Registration number:** NCT00158756 **Source of funding:** GlaxoSmithKline

RV1 NCT00289172

Trial name or title	"A Multicenter Study of the Immunogenicity & Safety of 2 Doses of GSK Biologicals' Oral Live Attenuated Human Rotavirus Vaccine (RIX4414) as Primary Dosing of Healthy Infants in India Aged Approximately 8 Wks at the Time of the First Dose"
Methods	"Prevention, Randomized, Double-Blind, Parallel Assignment, Safety Study"
Participants	**Number:** 360 **Description:** healthy infants in India aged 8 to 10 weeks at time of first vaccination
Interventions	1. Human rotavirus [RV1] vaccine 2. Placebo Both administered starting at age 8 to 12 weeks of age, according to a 2- dose schedule (0, 1 months schedule) Participants should have been administered the first dose of diphtheria, pertussis, and tetanus/ oral polio vaccine/Hepatitis B vaccines as per the local universal immunization program at 6 weeks of age
Outcomes	1. Percentage of seroconversion (anti-rota serum immunoglobulin A (IgA)) (primary) 2. Fever, vomiting, diarrhoea 3. Solicited symptoms

RV1 NCT00289172 (*Continued*)

	4. Unsolicited events 5. Serious adverse events 6. Presence of rotavirus in gastroenteritis stools
Starting date	February 2006 **Status:** completed
Contact information	Not stated
Notes	**Location:** India **Registration number:** NCT00289172 **Source of funding:** GlaxoSmithKline

RV1 NCT00383903

Trial name or title	"A Study of the Safety, Reactogenicity and Immunogenicity of 2 or 3 Doses of GSK Biologicals' Oral Live Attenuated Human Rotavirus (HRV) Vaccine in Healthy Infants (Approximately 5-10 Weeks Old) in South Africa"
Methods	"Prevention, Randomized, Double-Blind, Parallel Assignment, Safety/Efficacy Study"
Participants	**Number:** 475 **Inclusion criteria:** healthy infants aged between 5 and 10 weeks with confirmed negative HIV status of the participant's mother
Interventions	Oral live attenuated human rotavirus vaccine: 2 or 3 doses ("to determine the appropriate regimen of GSK human rotavirus vaccine for concomitant administration with EPI vaccines")
Outcomes	1. Seroconversion after human rotavirus vaccination (primary) 2. Shedding 3. Serum anti-rota IgA antibody concentrations 4. Anti-polio 1, 2 and 3 seroprotection rates 5. Reactogenicity 6. Safety
Starting date	September 2003 **Status:** completed
Contact information	GSK Clinical Trials, GlaxoSmithKline
Notes	**Location:** South Africa **Registration number:** NCT00383903 **Source of funding:** GlaxoSmithKline

RV1 NCT00420316

Trial name or title	"To Assess Long-Term Efficacy & Safety of Subjects Approximately 3 Years After Priming With 2 Doses of GlaxoSmithKline (GSK) Biologicals' Oral Live Attenuated Human Rotavirus (HRV) Vaccine (Rotarix) in the Primary Vaccination Study (102247)"
Methods	"Prevention, Randomized, Open Label, Parallel Assignment, Safety/Efficacy Study"
Participants	**Number:** 2601 **Description:** male or female who has completed the second year efficacy follow-up of the primary vaccination study in Finland
Interventions	"To assess the long-term efficacy and safety of the subjects during the third year after priming with 2 doses of GSK Biologicals' oral live attenuated HRV [human rotavirus] vaccine (Rotarix) in the primary vaccination study (102247). The Rotarix vaccine was administered in the primary vaccination study. There was no vaccine/ intervention in this long-term efficacy study"
Outcomes	1. Any rotavirus gastroenteritis (primary) 2. Severe rotavirus gastroenteritis 3. Severe gastroenteritis 4. Mortality 5. Serious adverse events (full study) 6. Intussusception (retrospective)
Starting date	February 2007 **Anticipated completion date:** August 2007, completed
Contact information	GSK Clinical Trials, GlaxoSmithKline
Notes	**Location:** Finland **Registration number:** NCT00420316 **Source of funding:** GlaxoSmithKline

RV1 NCT00425737

Trial name or title	"A Study to Assess the Efficacy, Immunogenicity and Safety of Two Doses of Oral Live Attenuated Human Rotavirus (HRV) Vaccine (Rotarix) in Healthy Infants"
Methods	"Prevention, Randomized, Double-Blind, Placebo Control, Parallel Assignment, Safety/Efficacy Study"
Participants	**Number:** 405 **Description:** healthy infants aged 6 to 12 weeks
Interventions	1. Two doses of oral live attenuated human rotavirus vaccine
Outcomes	1. Rotavirus gastroenteritis 2. Severe rotavirus gastroenteritis 3. Solicited symptoms 4. Unsolicited adverse events 5. Serious adverse events

RV1 NCT00425737 (*Continued*)

	6. Presence of rotavirus antigen in stool samples 7. Immunogenicity
Starting date	August 2002 **Completion date:** December 2002
Contact information	Clinical Trials, GlaxoSmithKline
Notes	**Location:** Finland **Registration number:** NCT00425737 **Source of funding:** GlaxoSmithKline

RV1 NCT00429481

Trial name or title	"A Study to Assess the Efficacy, Immunogenicity and Safety of 2 Doses of Oral Live Attenuated Human Rotavirus Vaccine (Rotarix) at Different Viral Concentrations in Healthy Infants"
Methods	"Prevention, Randomized, Double-Blind, Placebo Control, Parallel Assignment, Safety/Efficacy Study"
Participants	**Number:** 2460 **Description:** healthy infants aged 11 to 17 weeks
Interventions	1. RV1: 2 doses (at different concentrations) 2. Placebo
Outcomes	1. Rotavirus gastroenteritis 2. Severe rotavirus gastroenteritis 3. Rotavirus IgA antibody titres 4. Solicited symptoms 5. Unsolicited adverse events 6. Serious adverse events
Starting date	December 2000 **Completion date:** not stated, completed
Contact information	Clinical Trials, GlaxoSmithKline
Notes	**Location:** Singapore **Registration number:** NCT00429481 **Source of funding:** GlaxoSmithKline

RV1 NCT01171963

Trial name or title	"Efficacy, Immunogenicity and Safety of Two Doses of GlaxoSmithKline (GSK) Biologicals' Oral Live Attenuated Liquid Human Rotavirus (HRV) Vaccine (444563), in Healthy Infants"
Methods	"Randomized, Efficacy Study, Parallel Assignment, Double Blind"
Participants	**Number:** 3250 **Description:** male or female infant of Chinese origin between, and including, 6 and 16 weeks of age at the time of the first vaccination
Interventions	Co-administered with Infanrix™ and oral poliovirus vaccine 1. GSK Biologicals' liquid human rotavirus vaccine 444563 2. Placebo
Outcomes	1. Severe rotavirus gastroenteritis caused by the circulating wild-type rotavirus strains 2. Anti-rotavirus Immunoglobulin A antibody concentrations 3. Any and hospitalized rotavirus gastroenteritis caused by circulating wild type rotavirus 4. Any and severe all cause gastroenteritis 5. Solicited symptoms 6. Serious adverse events 7. Unsolicited symptoms
Starting date	August 2010 **Estimated completion:** December 2011
Contact information	GSK Clinical Trials, GlaxoSmithKline
Notes	**Location:** China **Registration number:** NCT01171963 **Source of funding:** GlaxoSmithKline

RV1 NCT01199874

Trial name or title	"The Immunogenicity of Rotavirus Vaccine Under Different Age Schedules and the Impact of Withholding Breast Feeding Around the Time of Vaccination on the Immunogenicity of Rotarix Vaccine"
Methods	"Randomized, Efficacy Study, Parallel Assignment, Open Label"
Participants	**Number:** 1100 (target) **Description:** healthy infants, 6 weeks 0 days to 6 weeks 6 days age at the time of enrolment, free of chronic or serious medical condition as determined by history and physical exam at time of enrolment into in the study
Interventions	Rotavirus vaccine
Outcomes	1. Seropositivity as anti-rotavirus IgA concentration >/= 20 U/ml
Starting date	April 2011 **Estimated completion:** April 2012

RV1 NCT01199874 (*Continued*)

Contact information	S. Asad Ali, MBBS, Aga Khan University, asad.ali@aku.edu
Notes	**Location:** Pakistan **Registration number:** NCT01199874 **Source of funding:** Program for Appropriate Technology in Health

RV1 NCT01375647

Trial name or title	"Exploration of the biologic basis for underperformance of oral polio and rotavirus vaccines in Bangladesh (PROVIDE)"
Methods	"Randomized, single blind, efficacy study, factorial assignment"
Participants	**Number:** 700 **Description:** healthy infant aged 0 to 7 days
Interventions	1. RV1 2. RV1 + IPV 3. IPV
Outcomes	1. Differences in episodes of Rotavirus diarrhoea between rotavirus vaccinees and non-vaccinees 2. Immunogenicity measures-IgA response to rota and polio virus vaccines
Starting date	May 2011 **Estimated completion:** October 2014
Contact information	Masud Alam, M.D., masud@icddrb.org
Notes	**Location:** Bangladesh **Registration number:** NCT01375647 **Source of funding:** University of Vermont; Bill and Melinda Gates Foundation; Centers for Disease Control and Prevention; International Centre for Diarrhoeal Disease Research, Bangladesh

RV1 NCT01575197

Trial name or title	Evaluation of the human rotavirus vaccine when given at varying schedules in rural Ghana
Methods	Randomized, parallel assignment, open label
Participants	**Number:** 456 **Description:** healthy infants 42 days to 55 days at enrolment, free of chronic or serious medical condition
Interventions	1. RV1 at 6 and 10 weeks of age 2. RV1 at 10 and 14 weeks of age 3. RV1 at 6, 10 and 14 weeks of age

RV1 NCT01575197 (*Continued*)

Outcomes	1. IgA seroconversion 2. IgA GMT's 3. Vaccine-type rotavirus shedding in stool 4. Serious adverse events
Starting date	April 2012 **Estimated completion:** October 2012
Contact information	George E Armah, PhD; GArmah@noguchi.mimcom.org
Notes	**Location:** Ghana **Registration number:** NCT01575197 **Source of funding:** PATH

RV1 Tatochenko 2008

Trial name or title	Co-administration of a human rotavirus vaccine Rix4414 with DTPw-HBv Vaccines: immunogenicity and reactogenicity in healthy infants
Methods	Randomized controlled trial
Participants	**Number:** 308 **Description:** healthy infants 11 to 17 weeks of age
Interventions	1. RIX4414 vaccine 2. Placebo
Outcomes	1. Immunogenicity 2. Safety
Starting date	Not reported
Contact information	GlaxoSmithKline
Notes	**Location:** not reported **Registration number:** not reported **Source of funding:** GlaxoSmithKline

RV5 NCT00880698

Trial name or title	"Safety and Immunogenicity of a Live, Attenuated Rotavirus (RotaTeq) in HIV-1 Infected and Uninfected Children Born to HIV-1-Infected Mothers"
Methods	"Randomized, Double Blind (Subject, Investigator), Parallel Assignment, Safety/Efficacy Study"

RV5 NCT00880698 (*Continued*)

Participants	**Number:** 320 **Description:** HIV-1 uninfected children (Group 1) and infected children (Group 2), up to 14 weeks, born to HIV-1-infected mothers
Interventions	1. RV5 2. Placebo
Outcomes	1. Safety 2. Immunogenicity
Starting date	December 2009 **Anticipated completion date:** July 2012 (final data collection date for primary outcome measure)
Contact information	Myron J Levin (Study Chair), University of Colorado at Denver Health Sciences Center
Notes	**Location:** Botswana **Registration number:** NCT00880698 **Source of funding:** National Institute of Allergy and Infectious Diseases (NIAID)

DATA AND ANALYSES

Comparison 1. RV1 versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rotavirus diarrhoea: severe (up to 1 year follow-up)	9	46045	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.11, 0.35]
1.1 Low-mortality countries (WHO strata A & B)	6	40631	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.07, 0.26]
1.2 High-mortality countries (WHO stratum E)	3	5414	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.18, 0.75]
2 Rotavirus diarrhoea: severe (up to 2 years follow-up)	10	35618	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.19, 0.29]
2.1 Low-mortality countries (WHO strata A & B)	8	32854	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.12, 0.20]
2.2 High-mortality countries (WHO stratum E)	2	2764	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.42, 0.79]
3 All-cause diarrhoea: severe cases (up to 1 year follow-up)	3	8813	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.42, 0.83]
3.1 Low-mortality countries (WHO strata A & B)	1	3874	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.37, 0.61]
3.2 High-mortality countries (WHO stratum E)	2	4939	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.44, 0.98]
4 All-cause diarrhoea: severe cases (up to 2 years follow-up)	4	9033	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.60, 0.76]
4.1 Low-mortality countries (WHO strata A & B)	2	6269	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.40, 0.60]
4.2 High-mortality countries (WHO stratum E)	2	2764	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.71, 0.95]
5 All-cause diarrhoea: severe episodes (up to 1 year follow-up)	1		Rate Ratio (Fixed, 95% CI)	Subtotals only
5.1 Low-mortality countries (WHO strata A & B)	1		Rate Ratio (Fixed, 95% CI)	0.60 [0.50, 0.72]
6 All-cause diarrhoea: severe episodes (up to 2 years follow-up)	2		Rate Ratio (Fixed, 95% CI)	Subtotals only
6.1 Low-mortality countries (WHO strata A & B)	2		Rate Ratio (Fixed, 95% CI)	0.63 [0.56, 0.71]
7 All-cause death	25	100802	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.82, 1.32]
7.1 Low-mortality countries (WHO strata A & B)	18	93321	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.89, 1.81]
7.2 High-mortality countries (WHO strata D & E)	7	7481	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.64, 1.22]
8 All serious adverse events	27	99438	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.85, 0.95]
8.1 Low-mortality countries (WHO strata A & B)	20	91957	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.84, 0.95]

8.2 High-mortality countries (WHO strata D & E)	7	7481	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.76, 1.04]
9 Serious adverse events: intussusception	13	97246	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.53, 1.47]
9.1 Low-mortality countries (WHO strata A & B)	11	91832	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.52, 1.46]
9.2 High-mortality countries (WHO stratum E)	2	5414	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.06, 36.63]
10 Serious adverse events: Kawasaki disease	3	13117	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [0.30, 10.61]
11 Serious adverse events requiring hospitalization	2	63675	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.81, 0.96]
12 Rotavirus diarrhoea: of any severity (up to 2 months follow-up)	11	3610	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.69, 2.00]
12.1 Low-mortality countries (WHO strata A & B)	8	2853	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.66, 2.50]
12.2 High-mortality countries (WHO strata D & E)	3	757	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.41, 2.41]
13 Rotavirus diarrhoea: of any severity (up to 1 year follow-up)	6	11349	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.19, 0.50]
13.1 Low-mortality countries (WHO strata A & B)	3	5935	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.08, 0.47]
13.2 High-mortality countries (WHO stratum E)	3	5414	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.28, 0.73]
14 Rotavirus diarrhoea: of any severity (up to 2 years follow-up)	6	8544	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.25, 0.48]
14.1 Low-mortality countries (WHO strata A & B)	5	7293	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.21, 0.50]
14.2 High-mortality countries (WHO stratum E)	1	1251	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.28, 0.62]
15 All-cause diarrhoea: all cases (up to 2 months follow-up)	6	2448	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.71, 1.13]
15.1 Low-mortality countries (WHO strata A & B)	5	2348	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.66, 1.12]
15.2 High-mortality countries (WHO stratum E)	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.69, 1.58]
16 All-cause diarrhoea: all cases (up to 1 year follow-up)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 Low-mortality countries (WHO strata A & B)	2	2204	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.82, 1.03]
17 All-cause diarrhoea: all cases (up to 2 years follow-up)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 Low-mortality countries (WHO strata A & B)	2	2789	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.66, 1.00]
18 All-cause diarrhoea: all episodes (up to 1 year follow-up)	2		Rate Ratio (Fixed, 95% CI)	Subtotals only
18.1 Low-mortality countries (WHO strata A & B)	2		Rate Ratio (Fixed, 95% CI)	0.98 [0.88, 1.10]

19 All-cause diarrhoea: all episodes (up to 2 years follow-up)	1		Rate Ratio (Fixed, 95% CI)	Subtotals only
19.1 Low-mortality countries (WHO strata A & B)	1		Rate Ratio (Fixed, 95% CI)	1.02 [0.78, 1.33]
20 All-cause hospitalizations (up to 2 years follow-up)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 Low-mortality countries (WHO strata A & B)	1	2421	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.15, 0.86]
21 Rotavirus diarrhoea: requiring hospitalization	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
21.1 Up to 1 year follow-up (at least 1 rotavirus season)	6	39260	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.08, 0.43]
21.2 Second year follow-up (at least 2 rotavirus seasons)	6	32183	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.09, 0.23]
22 Rotavirus diarrhoea: requiring medical attention	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 Up to 1 year follow-up (at least 1 rotavirus season)	1	3874	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.04, 0.16]
22.2 Second year follow-up (at least 2 rotavirus seasons)	3	7017	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.16, 0.31]
23 All-cause diarrhoea: cases requiring hospitalization	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
23.1 Up to one year of follow-up (at least 1 rotavirus season)	2	14393	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.17, 1.11]
23.2 Second year of follow-up (at least 2 rotavirus seasons)	2	14367	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.27, 0.99]
24 All-cause diarrhoea: episodes requiring hospitalization	1		Rate Ratio (Fixed, 95% CI)	Subtotals only
24.1 Up to 1 year of follow-up (at least 1 rotavirus season)	1		Rate Ratio (Fixed, 95% CI)	0.58 [0.47, 0.71]
24.2 Second year of follow-up (at least 2 rotavirus seasons)	1		Rate Ratio (Fixed, 95% CI)	0.53 [0.46, 0.61]
25 Reactogenicity: fever	23		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
25.1 After dose 1	20	11563	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.98, 1.18]
25.2 After dose 2	19	11156	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.91, 1.06]
25.3 After dose 3	4	1390	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.86, 1.13]
25.4 End of follow-up	16	8799	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.93, 1.01]
26 Reactogenicity: diarrhoea	22		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
26.1 After dose 1	20	14103	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.86, 1.20]
26.2 After dose 2	19	11156	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.76, 1.14]
26.3 After dose 3	4	1390	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.35, 1.36]
26.4 End of follow-up	15	11178	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.80, 1.07]
27 Reactogenicity: vomiting	22		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
27.1 After dose 1	20	14103	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.96, 1.17]
27.2 After dose 2	19	11156	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.78, 1.09]
27.3 After dose 3	4	1390	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.71, 2.50]
27.4 End of follow-up	15	11178	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.82, 1.05]
28 Adverse events requiring discontinuation (end of follow-up)	21	90604	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.86, 1.34]

29 Immunogenicity: rotavirus vaccine shedding (end of follow-up)	15	2606	Risk Ratio (M-H, Random, 95% CI)	12.07 [5.23, 27.85]
30 Immunogenicity: seroconversion	24		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
30.1 After dose 1	9	2537	Risk Ratio (M-H, Random, 95% CI)	20.39 [8.48, 49.01]
30.2 After dose 2	21	6416	Risk Ratio (M-H, Random, 95% CI)	11.04 [7.03, 17.34]
30.3 After dose 3	4	1094	Risk Ratio (M-H, Random, 95% CI)	8.43 [4.16, 17.11]
31 Drop outs before the end of the trial	22	25005	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.81, 1.02]
32 Subgroup analysis: rotavirus diarrhoea of any severity (by G type)	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
32.1 G1	4	24335	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.08, 0.26]
32.2 G2	3	23587	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.24, 0.75]
32.3 G3	2	5720	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.05, 0.48]
32.4 G4	2	5720	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.07, 0.59]
32.5 G9	2	5720	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.17, 0.91]
33 Subgroup analysis: severe cases of rotavirus diarrhoea (by G type)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
33.1 G1	5	36100	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.11, 0.37]
33.2 G2	4	37117	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.16, 0.98]
33.3 G3	2	12940	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.01, 8.16]
33.4 G4	1	2421	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.00, 2.95]
33.5 G9	3	19250	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.07, 0.33]
34 Subgroup analysis: rotavirus diarrhoea in malnourished children	1	287	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.19, 0.79]
34.1 Up to 1 year of follow-up (at least 1 rotavirus season)	1	287	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.19, 0.79]
35 Subgroup analysis: rotavirus diarrhoea in HIV-infected children	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.26, 3.78]
36 Subgroup analysis: serious adverse events in premature babies	1	1009	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.45, 1.25]
37 Subgroup analysis: severe rotavirus diarrhoea in breast fed and formula fed infants	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
37.1 Severe rotavirus diarrhoea (2 year follow-up) breast fed infants	1	3046	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.06, 0.14]
37.2 Severe rotavirus diarrhoea (2 year follow-up): formula fed infants	1	828	Risk Ratio (M-H, Fixed, 95% CI)	0.02 [0.00, 0.14]
38 Sensitivity analysis: allocation concealment	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
38.1 Rotavirus diarrhoea: severe, up to 1 year follow-up (low-mortality countries)	4	32475	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.04, 0.23]

38.2 Rotavirus diarrhoea: severe, up to 1 year follow-up (high-mortality countries)	2	4939	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.15, 0.88]
38.3 All-cause diarrhoea: severe, up to 1 year follow-up (high-mortality countries)	2	4939	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.44, 0.98]

Comparison 2. RV5 versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rotavirus diarrhoea: severe (up to 1 year follow-up)	7	8260	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.26, 0.53]
1.1 Low-mortality countries (WHO strata A & B)	3	2344	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.04, 0.45]
1.2 High-mortality countries (WHO strata D & E)	4	5916	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.29, 0.62]
2 Rotavirus diarrhoea: severe (up to 2 years follow-up)	7	9075	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.30, 0.70]
2.1 Low-mortality countries (WHO strata A & B)	3	3190	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.07, 0.50]
2.2 High-mortality countries (WHO strata D & E)	4	5885	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.43, 0.82]
3 All-cause diarrhoea: severe cases (up to 1 year follow-up)	4	5114	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.39, 1.06]
3.1 Low-mortality countries (WHO stratum A)	1	1029	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.16, 0.48]
3.2 High-mortality countries (WHO strata D & E)	3	4085	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.58, 1.11]
4 All-cause diarrhoea: severe cases (up to 2 years follow-up)	5	7006	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.73, 0.96]
4.1 Low-mortality countries (WHO strata A & B)	1	1029	Risk Ratio (M-H, Fixed, 95% CI)	0.04 [0.00, 0.70]
4.2 High-mortality countries (WHO strata D & E)	4	5977	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.75, 0.98]
5 All-cause death	12	80207	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.75, 1.28]
5.1 Low-mortality countries (WHO strata A & B)	8	73603	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.67, 2.08]
5.2 High-mortality countries (WHO strata D & E)	4	6604	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.69, 1.25]
6 All serious adverse events	11	78226	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.85, 1.01]
6.1 Low-mortality countries (WHO strata A & B)	7	71638	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.84, 1.01]
6.2 High-mortality countries (WHO strata D & E)	4	6588	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.66, 1.33]
7 Serious adverse events: intussusception	15	81462	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.34, 1.31]

7.1 Low-mortality countries (WHO strata A & B)	11	74874	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.34, 1.31]
7.2 High-mortality countries (WHO strata D & E)	4	6588	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Rotavirus diarrhoea: of any severity (up to 1 year follow-up)	7	12420	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.26, 0.52]
8.1 Low-mortality countries (WHO strata A & B)	4	7614	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.22, 0.33]
8.2 High-mortality countries (WHO strata D & E)	3	4806	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.28, 0.94]
9 Rotavirus diarrhoea: of any severity (up to 2 years follow-up)	6	9024	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.36, 0.70]
9.1 Low-mortality countries (WHO strata A & B)	2	2280	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.25, 0.50]
9.2 High-mortality countries (WHO strata D & E)	4	6744	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.45, 0.83]
10 All-cause diarrhoea: of any severity (up to 1 year follow-up)	2	2089	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.51, 0.81]
10.1 Low-mortality countries (WHO strata A & B)	1	1030	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.28, 0.60]
10.2 High-mortality countries (WHO stratum E)	1	1059	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.61, 1.11]
11 All-cause diarrhoea: of any severity (up to 2 years follow-up)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 High-mortality countries (WHO stratum E)	1	1059	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.68, 1.16]
12 Rotavirus diarrhoea: requiring hospitalization	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Up to 1 year of follow-up	1	57134	Risk Ratio (M-H, Fixed, 95% CI)	0.04 [0.02, 0.10]
13 Rotavirus diarrhoea: requiring medical attention	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 Up to 1 year of follow-up	1	57134	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.04, 0.12]
14 Reactogenicity: fever	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 After dose 1	3	3090	Risk Ratio (M-H, Random, 95% CI)	1.28 [1.04, 1.58]
14.2 After dose 2	1	417	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.47, 1.19]
14.3 After dose 3	1	416	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.77, 1.59]
14.4 End of follow-up	7	14067	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.93, 1.15]
15 Reactogenicity: diarrhoea	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 After dose 1	1	711	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.71, 1.39]
15.2 End of follow-up	6	12763	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.98, 1.12]
16 Reactogenicity: vomiting	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 After dose 1	1	711	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.59, 1.29]
16.2 End of follow-up	5	11970	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.91, 1.09]
17 Adverse events requiring discontinuation (end of follow-up)	9	11437	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.38, 1.19]
18 Immunogenicity: rotavirus vaccine shedding (after dose 3)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

19 Immunogenicity: seroconversion (after dose 3)	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
20 Drop outs before the end of the trial	10	81573	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.88, 1.07]
21 Subgroup analysis: rotavirus diarrhoea of any severity (by G type)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
21.1 G1	3	7158	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.21, 0.33]
21.2 G2	2	6043	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.16, 0.88]
21.3 G3	3	7158	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.03, 2.29]
21.4 G4	2	6043	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.13, 1.67]
21.5 G9	1	5673	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.03, 3.21]
22 Subgroup analysis: severe cases of rotavirus diarrhoea (by G type)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
22.1 G1	2	72743	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.01, 2.97]
22.2 G2	2	72743	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.08, 2.09]
22.3 G3	2	72743	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.03, 1.06]
22.4 G4	2	72743	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.03, 0.48]
22.5 G9	2	72743	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.01, 2.37]
23 Subgroup analysis: HIV-infected children	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
23.1 Rotavirus diarrhoea: severe (up to two years follow-up)	1	38	Risk Ratio (M-H, Fixed, 95% CI)	2.45 [0.11, 56.68]
23.2 All-cause diarrhoea: severe (up to two years follow-up)	1	38	Risk Ratio (M-H, Fixed, 95% CI)	4.05 [0.52, 31.43]
23.3 All-cause death	1	38	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [0.59, 4.47]
23.4 Serious adverse events (up to 14 days after each dose)	1	37	Risk Ratio (M-H, Fixed, 95% CI)	1.90 [0.42, 8.58]
24 Subgroup analysis: rotavirus diarrhoea of any severity in premature babies (1 year follow-up)	1	170	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.15, 1.06]
25 Sensitivity analysis: allocation concealment	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
25.1 Rotavirus diarrhoea: severe, up to 2 years follow-up (high-mortality countries)	3	4748	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.44, 0.87]
25.2 All-cause diarrhoea: severe, up to 1 year follow-up (high-mortality countries)	2	3127	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.49, 1.21]

Analysis 1.1. Comparison 1 RV1 versus placebo, Outcome 1 Rotavirus diarrhoea: severe (up to 1 year follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 1 Rotavirus diarrhoea: severe (up to 1 year follow-up)

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low-mortality countries (WHO strata A & B)					
RV1 Bernstein 1999-USA	2/108	9/107		7.6 %	0.22 [0.05, 1.00]
RV1 GSK[024] 2008-LA	7/4211	19/2099		11.9 %	0.18 [0.08, 0.44]
RV1 Phua 2009-AS	0/5263	15/5256		3.2 %	0.03 [0.00, 0.54]
RV1 Ruiz-Palac 06-LA/EU (1)	12/9009	77/8858		13.8 %	0.15 [0.08, 0.28]
RV1 Salinas 2005-LA	27/1392	34/454		14.6 %	0.26 [0.16, 0.42]
RV1 Vesikari 2007a-EU	5/2572	60/1302		11.5 %	0.04 [0.02, 0.10]
Subtotal (95% CI)	**22555**	**18076**		**62.6 %**	**0.14 [0.07, 0.26]**
Total events: 53 (RV1), 214 (Placebo)					
Heterogeneity: Tau^2 = 0.35; Chi^2 = 14.68, df = 5 (P = 0.01); I^2 =66%					
Test for overall effect: Z = 6.14 (P < 0.00001)					
2 High-mortality countries (WHO stratum E)					
RV1 Madhi 2010-MWI (2)	52/1182	47/591		15.3 %	0.55 [0.38, 0.81]
RV1 Madhi 2010-ZAF (3)	16/2116	36/1050		14.0 %	0.22 [0.12, 0.40]
RV1 Steele 2010b-ZAF	5/379	3/96		8.1 %	0.42 [0.10, 1.74]
Subtotal (95% CI)	**3677**	**1737**		**37.4 %**	**0.37 [0.18, 0.75]**
Total events: 73 (RV1), 86 (Placebo)					
Heterogeneity: Tau^2 = 0.25; Chi^2 = 6.70, df = 2 (P = 0.04); I^2 =70%					
Test for overall effect: Z = 2.74 (P = 0.0061)					
Total (95% CI)	**26232**	**19813**		**100.0 %**	**0.20 [0.11, 0.35]**
Total events: 126 (RV1), 300 (Placebo)					
Heterogeneity: Tau^2 = 0.51; Chi^2 = 39.36, df = 8 (P<0.00001); I^2 =80%					
Test for overall effect: Z = 5.61 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 4.15, df = 1 (P = 0.04), I^2 =76%					

(1) This multinational study includes 12 Latin America countries, two of them with high mortality (Nicaragua and Peru)

(2) Data taken from main paper Supplementary Appendix, Table 3 - total vaccinated cohort in Malawi

(3) Data taken from main paper Supplementary Appendix, Table 3 - total vaccinated cohort in South Africa

Analysis 1.2. Comparison 1 RV1 versus placebo, Outcome 2 Rotavirus diarrhoea: severe (up to 2 years follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 2 Rotavirus diarrhoea: severe (up to 2 years follow-up)

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-mortality countries (WHO strata A % B)					
RV1 Bernstein 1999-USA	3/108	19/107		4.3 %	0.16 [0.05, 0.51]
RV1 Kawamura 2010-JPN	2/498	12/250		3.6 %	0.08 [0.02, 0.37]
RV1 Phua 2005-SGP	0/1779	1/642		0.5 %	0.12 [0.00, 2.95]
RV1 Phua 2009-AS	2/5263	51/5256		11.4 %	0.04 [0.01, 0.16]
RV1 Ruiz-Palac 06-LA/EU (1)	32/7205	161/7081		36.3 %	0.20 [0.13, 0.29]
RV1 Salinas 2005-LA	2/332	3/109		1.0 %	0.22 [0.04, 1.29]
RV1 Vesikari 2004b-FIN	3/245	10/123		3.0 %	0.15 [0.04, 0.54]
RV1 Vesikari 2007a-EU	19/2554	67/1302		19.9 %	0.14 [0.09, 0.24]
Subtotal (95% CI)	**17984**	**14870**		**79.9 %**	**0.15 [0.12, 0.20]**
Total events: 63 (RV1), 324 (Placebo)					
Heterogeneity: Chi² = 6.09, df = 7 (P = 0.53); I² =0.0%					
Test for overall effect: Z = 13.65 (P < 0.00001)					
2 High-mortality countries (WHO stratum E)					
RV1 Madhi 2010-MWI (2)	70/1030	53/483		16.1 %	0.62 [0.44, 0.87]
RV1 Madhi 2010-ZAF (3)	11/843	13/408		3.9 %	0.41 [0.19, 0.91]
Subtotal (95% CI)	**1873**	**891**		**20.1 %**	**0.58 [0.42, 0.79]**
Total events: 81 (RV1), 66 (Placebo)					
Heterogeneity: Chi² = 0.88, df = 1 (P = 0.35); I² =0.0%					
Test for overall effect: Z = 3.44 (P = 0.00058)					
Total (95% CI)	**19857**	**15761**		**100.0 %**	**0.24 [0.19, 0.29]**
Total events: 144 (RV1), 390 (Placebo)					
Heterogeneity: Chi² = 46.39, df = 9 (P<0.00001); I² =81%					
Test for overall effect: Z = 14.18 (P < 0.00001)					
Test for subgroup differences: Chi² = 40.38, df = 1 (P = 0.00), I² =98%					

(1) This multinational study includes 12 Latin America countries, two of them with high mortality (Nicaragua and Peru)

(2) Data from Malawi cohort only

(3) Assessment of vaccine effiicacy up to two years follow-up available from cohort 2 subjects only in South Africa

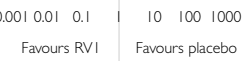
Analysis 1.3. Comparison 1 RV1 versus placebo, Outcome 3 All-cause diarrhoea: severe cases (up to 1 year follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 3 All-cause diarrhoea: severe cases (up to 1 year follow-up)

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low-mortality countries (WHO strata A & B)					
RV1 Vesikari 2007a-EU	116/2572	123/1302		33.1 %	0.48 [0.37, 0.61]
Subtotal (95% CI)	**2572**	**1302**		**33.1 %**	**0.48 [0.37, 0.61]**
Total events: 116 (RV1), 123 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.92 (P < 0.00001)					
2 High-mortality countries (WHO stratum E)					
RV1 Madhi 2010-MWI (1)	221/1182	139/591		35.7 %	0.79 [0.66, 0.96]
RV1 Madhi 2010-ZAF (2)	92/2116	86/1050		31.2 %	0.53 [0.40, 0.71]
Subtotal (95% CI)	**3298**	**1641**		**66.9 %**	**0.66 [0.44, 0.98]**
Total events: 313 (RV1), 225 (Placebo)					
Heterogeneity: Tau^2 = 0.07; Chi^2 = 5.42, df = 1 (P = 0.02); I^2 =82%					
Test for overall effect: Z = 2.06 (P = 0.039)					
Total (95% CI)	**5870**	**2943**		**100.0 %**	**0.59 [0.42, 0.83]**
Total events: 429 (RV1), 348 (Placebo)					
Heterogeneity: Tau^2 = 0.07; Chi^2 = 12.28, df = 2 (P = 0.002); I^2 =84%					
Test for overall effect: Z = 3.03 (P = 0.0024)					
Test for subgroup differences: Chi^2 = 1.85, df = 1 (P = 0.17), I^2 =46%					



(1) Data taken from main paper Supplementary Appendix, Table 6 - total vaccinated cohort in Malawi

(2) Data taken from main paper Supplementary Appendix, Table 6 - total vaccinated cohort in South Africa

Analysis 1.4. Comparison 1 RV1 versus placebo, Outcome 4 All-cause diarrhoea: severe cases (up to 2 years follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 4 All-cause diarrhoea: severe cases (up to 2 years follow-up)

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-mortality countries (WHO strata A % B)					
RV1 Phua 2005-SGP	11/1779	10/642		2.9 %	0.40 [0.17, 0.93]
RV1 Vesikari 2007a-EU	149/2554	153/1294		40.6 %	0.49 [0.40, 0.61]
Subtotal (95% CI)	**4333**	**1936**		**43.5 %**	**0.49 [0.40, 0.60]**
Total events: 160 (RV1), 163 (Placebo)					
Heterogeneity: Chi^2 = 0.24, df = 1 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 6.76 (P < 0.00001)					
2 High-mortality countries (WHO stratum E)					
RV1 Madhi 2010-MWI (1)	287/1030	160/483		43.5 %	0.84 [0.72, 0.99]
RV1 Madhi 2010-ZAF (2)	76/843	48/408		12.9 %	0.77 [0.54, 1.08]
Subtotal (95% CI)	**1873**	**891**		**56.5 %**	**0.82 [0.71, 0.95]**
Total events: 363 (RV1), 208 (Placebo)					
Heterogeneity: Chi^2 = 0.24, df = 1 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 2.60 (P = 0.0093)					
Total (95% CI)	**6206**	**2827**		**100.0 %**	**0.68 [0.60, 0.76]**
Total events: 523 (RV1), 371 (Placebo)					
Heterogeneity: Chi^2 = 17.33, df = 3 (P = 0.00060); I^2 =83%					
Test for overall effect: Z = 6.41 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 16.39, df = 1 (P = 0.00), I^2 =94%					

(1) Data from Malawi cohort only

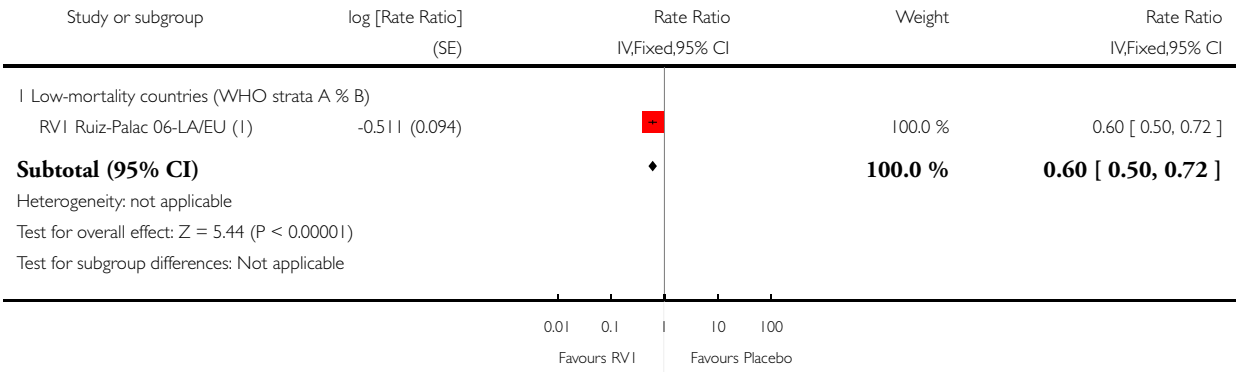
(2) Data from South Africa cohort only

Analysis 1.5. Comparison 1 RV1 versus placebo, Outcome 5 All-cause diarrhoea: severe episodes (up to 1 year follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 5 All-cause diarrhoea: severe episodes (up to 1 year follow-up)



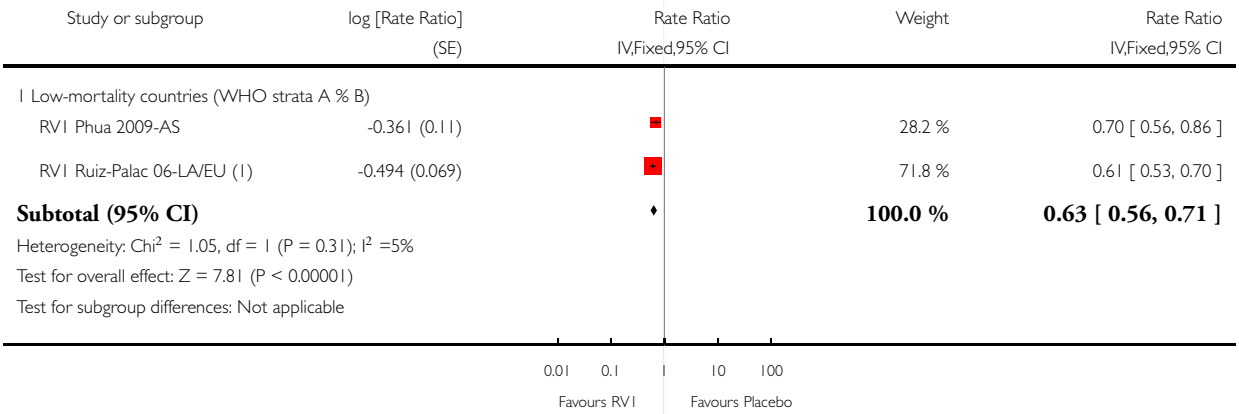
(1) This multinational study includes 12 Latin America countries, two of them with high mortality (Nicaragua and Peru)

Analysis 1.6. Comparison 1 RV1 versus placebo, Outcome 6 All-cause diarrhoea: severe episodes (up to 2 years follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 6 All-cause diarrhoea: severe episodes (up to 2 years follow-up)



(1) This multinational study includes 12 Latin America countries, two of them with high mortality (Nicaragua and Peru)

Analysis 1.7. Comparison 1 RV1 versus placebo, Outcome 7 All-cause death.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 7 All-cause death

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Low-mortality countries (WHO strata A % B)				
RV1 Anh 2011-PHL	1/281	0/64		0.69 [0.03, 16.78]
RV1 Anh 2011-VNM	0/279	0/73		0.0 [0.0, 0.0]
RV1 Bernstein 1999-USA	1/108	0/107		2.97 [0.12, 72.16]
RV1 GSK[021] 2007-PAN	0/177	0/51		0.0 [0.0, 0.0]
RV1 GSK[024] 2008-LA	10/4376	2/2192		2.50 [0.55, 11.42]
RV1 GSK[041] 2007-KOR	0/103	0/52		0.0 [0.0, 0.0]
RV1 GSK[101555] 2008-PHL	0/100	0/50		0.0 [0.0, 0.0]
RV1 Kawamura 2010-JPN	0/507	0/257		0.0 [0.0, 0.0]
RV1 Kerdpanich 2010-THA	0/395	0/26		0.0 [0.0, 0.0]
RV1 Omenaca 2012-EU	0/670	1/339		0.17 [0.01, 4.14]
RV1 Phua 2005-SGP	3/1779	0/642		2.53 [0.13, 48.89]
RV1 Phua 2009-AS	1/5263	3/5256		0.33 [0.03, 3.20]
RV1 Rivera 2011-DOM	0/100	0/100		0.0 [0.0, 0.0]
RV1 Ruiz-Palac 06-LA/EU (1)	56/31673	43/31552		1.30 [0.87, 1.93]
RV1 Salinas 2005-LA	2/1618	1/537		0.66 [0.06, 7.31]
RV1 Vesikari 2004b-FIN	0/267	0/133		0.0 [0.0, 0.0]
RV1 Vesikari 2007a-EU	0/2613	0/1331		0.0 [0.0, 0.0]
RV1 Vesikari 2011-FIN	0/200	0/50		0.0 [0.0, 0.0]
Subtotal (95% CI)	**50509**	**42812**		**1.27 [0.89, 1.81]**
Total events: 74 (RV1), 50 (Placebo)				
Heterogeneity: Chi^2 = 4.56, df = 7 (P = 0.71); I^2 =0.0%				

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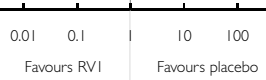
Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 1.30 (P = 0.19)				
2 High-mortality countries (WHO strata D % E)				
RV1 GSK[033] 2007-LA (2)	3/730	0/124		1.20 [0.06, 23.03]
RV1 Madhi 2010-AF	83/3298	43/1641		0.96 [0.67, 1.38]
RV1 Narang 2009-IND	0/182	0/181		0.0 [0.0, 0.0]
RV1 Steele 2008-ZAF	3/300	5/150		0.30 [0.07, 1.24]
RV1 Steele 2010a-ZAF	6/50	9/50		0.67 [0.26, 1.73]
RV1 Steele 2010b-ZAF	3/379	0/96		1.79 [0.09, 34.30]
RV1 Zaman 2009-BGD	1/200	0/100		1.51 [0.06, 36.68]
Subtotal (95% CI)	**5139**	**2342**		**0.88 [0.64, 1.22]**
Total events: 99 (RV1), 57 (Placebo)				
Heterogeneity: Chi^2 = 3.13, df = 5 (P = 0.68); I^2 =0.0%				
Test for overall effect: Z = 0.76 (P = 0.45)				
Total (95% CI)	**55648**	**45154**		**1.04 [0.82, 1.32]**
Total events: 173 (RV1), 107 (Placebo)				
Heterogeneity: Chi^2 = 9.82, df = 13 (P = 0.71); I^2 =0.0%				
Test for overall effect: Z = 0.36 (P = 0.72)				
Test for subgroup differences: Chi^2 = 2.17, df = 1 (P = 0.14), I^2 =54%				



(1) This multinational study includes 12 Latin America countries, two of them with high mortality (Nicaragua and Peru)

(2) This study was conducted in four study centres in a high mortality country (Peru), but also in three study centres in two low mortality countries (Colombia and Mexico)

Analysis 1.8. Comparison 1 RV1 versus placebo, Outcome 8 All serious adverse events.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 8 All serious adverse events

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Low-mortality countries (WHO strata A % B)				
RV1 Anh 2011-PHL	1/281	1/64		0.23 [0.01, 3.59]
RV1 Anh 2011-VNM	15/279	1/73		3.92 [0.53, 29.23]
RV1 Bernstein 1998-USA	0/21	0/20		0.0 [0.0, 0.0]
RV1 Dennehy 2005-NA	15/421	8/108		0.48 [0.21, 1.10]
RV1 GSK[021] 2007-PAN	18/177	9/51		0.58 [0.28, 1.20]
RV1 GSK[024] 2008-LA	505/4376	265/2192		0.95 [0.83, 1.10]
RV1 GSK[041] 2007-KOR	0/103	0/52		0.0 [0.0, 0.0]
RV1 GSK[101555] 2008-PHL	5/100	0/50		5.55 [0.31, 98.50]
RV1 Kawamura 2010-JPN	72/508	44/257		0.83 [0.59, 1.17]
RV1 Kerdpanich 2010-THA	11/396	4/51		0.35 [0.12, 1.07]
RV1 Omenaca 2012-EU	34/670	23/339		0.75 [0.45, 1.25]
RV1 Phua 2005-SGP	144/1811	40/653		1.30 [0.93, 1.82]
RV1 Phua 2009-AS	10/4272	11/4226		0.90 [0.38, 2.12]
RV1 Rivera 2011-DOM	5/100	6/100		0.83 [0.26, 2.64]
RV1 Ruiz-Palac 06-LA/EU (1)	928/31673	1047/31552		0.88 [0.81, 0.96]
RV1 Salinas 2005-LA	156/1618	64/537		0.81 [0.62, 1.06]
RV1 Vesikari 2004a-FIN	2/128	1/64		1.00 [0.09, 10.82]
RV1 Vesikari 2004b-FIN	28/267	9/133		1.55 [0.75, 3.19]
RV1 Vesikari 2007a-EU	290/2646	176/1348		0.84 [0.70, 1.00]
RV1 Vesikari 2011-FIN	3/193	0/47		1.73 [0.09, 32.97]
Subtotal (95% CI)	**50040**	**41917**		**0.90 [0.84, 0.95]**
Total events: 2242 (RV1), 1709 (Placebo)				
Heterogeneity: Chi^2 = 20.49, df = 17 (P = 0.25); I^2 =17%				
Test for overall effect: Z = 3.43 (P = 0.00061)				
2 High-mortality countries (WHO strata D % E)				
RV1 GSK[033] 2007-LA (2)	3/730	0/124		1.20 [0.06, 23.03]

0.001 0.01 0.1 1 10 100 1000

Favours RV1 Favours placebo

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Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
RV1 Madhi 2010-AF	319/3298	189/1641		0.84 [0.71, 1.00]
RV1 Narang 2009-IND	3/182	2/181		1.49 [0.25, 8.82]
RV1 Steele 2008-ZAF	30/300	14/150		1.07 [0.59, 1.96]
RV1 Steele 2010a-ZAF	17/50	12/50		1.42 [0.76, 2.65]
RV1 Steele 2010b-ZAF	19/379	5/96		0.96 [0.37, 2.51]
RV1 Zaman 2009-BGD	1/200	0/100		1.51 [0.06, 36.68]
Subtotal (95% CI)	**5139**	**2342**		**0.89 [0.76, 1.04]**
Total events: 392 (RV1), 222 (Placebo)				
Heterogeneity: Chi^2 = 3.42, df = 6 (P = 0.75); I^2 =0.0%				
Test for overall effect: Z = 1.50 (P = 0.13)				
Total (95% CI)	**55179**	**44259**		**0.90 [0.85, 0.95]**
Total events: 2634 (RV1), 1931 (Placebo)				
Heterogeneity: Chi^2 = 23.90, df = 24 (P = 0.47); I^2 =0.0%				
Test for overall effect: Z = 3.74 (P = 0.00019)				
Test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.91), I^2 =0.0%				

(1) This multinational study includes 12 Latin America countries, two of them with high mortality (Nicaragua and Peru)

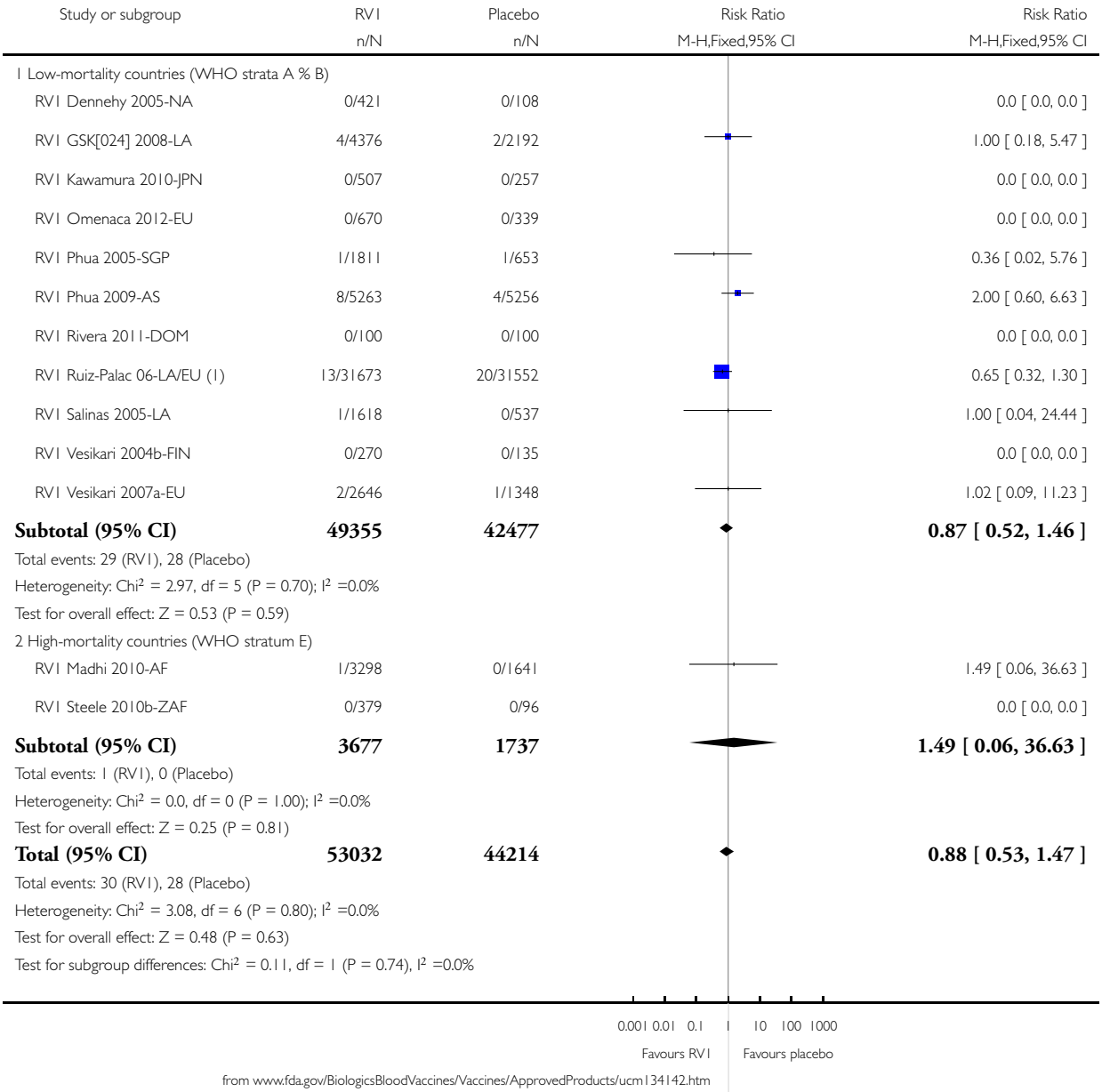
(2) This study was conducted in four study centres in a high mortality country (Peru), but also in three study centres in two low mortality countries (Colombia and Mexico)

Analysis 1.9. Comparison 1 RV1 versus placebo, Outcome 9 Serious adverse events: intussusception.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 9 Serious adverse events: intussusception



from www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm134142.htm

(1) This multinational study includes 12 Latin America countries, two of them with high mortality (Nicaragua and Peru). Data updated

Analysis 1.10. Comparison 1 RV1 versus placebo, Outcome 10 Serious adverse events: Kawasaki disease.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 10 Serious adverse events: Kawasaki disease

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RV1 Phua 2005-SGP	2/1811	0/653		37.0 %	1.80 [0.09, 37.54]
RV1 Phua 2009-AS	1/4272	0/4226		25.3 %	2.97 [0.12, 72.83]
RV1 Salinas 2005-LA	1/1618	0/537		37.8 %	1.00 [0.04, 24.44]
Total (95% CI)	**7701**	**5416**		**100.0 %**	**1.79 [0.30, 10.61]**

Total events: 4 (RV1), 0 (Placebo)

Heterogeneity: $Chi^2 = 0.22$, df = 2 (P = 0.89); $I^2 = 0.0\%$

Test for overall effect: Z = 0.64 (P = 0.52)

Test for subgroup differences: Not applicable

Analysis 1.11. Comparison 1 RV1 versus placebo, Outcome 11 Serious adverse events requiring hospitalization.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 11 Serious adverse events requiring hospitalization

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RV1 Ruiz-Palac 06-LA/EU	886/31673	1003/31552		99.9 %	0.88 [0.81, 0.96]
RV1 Steele 2008-ZAF	1/300	0/150		0.1 %	1.50 [0.06, 36.72]
Total (95% CI)	**31973**	**31702**		**100.0 %**	**0.88 [0.81, 0.96]**

Total events: 887 (RV1), 1003 (Placebo)

Heterogeneity: $Chi^2 = 0.11$, df = 1 (P = 0.74); $I^2 = 0.0\%$

Test for overall effect: Z = 2.81 (P = 0.0050)

Test for subgroup differences: Not applicable

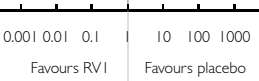
Analysis 1.12. Comparison 1 RV1 versus placebo, Outcome 12 Rotavirus diarrhoea: of any severity (up to 2 months follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 12 Rotavirus diarrhoea: of any severity (up to 2 months follow-up)

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Low-mortality countries (WHO strata A % B)				
RV1 Anh 2011-PHL	1/270	1/66		0.24 [0.02, 3.86]
RV1 Anh 2011-VNM	0/275	0/71		0.0 [0.0, 0.0]
RV1 GSK[041] 2007-KOR	1/103	1/52		0.50 [0.03, 7.91]
RV1 GSK[101555] 2008-PHL	4/100	1/50		2.00 [0.23, 17.43]
RV1 Kerdpanich 2010-THA	4/392	0/52		1.21 [0.07, 22.23]
RV1 Omenaca 2012-EU	3/670	2/339		0.76 [0.13, 4.52]
RV1 Rivera 2011-DOM	10/100	6/100		1.67 [0.63, 4.41]
RV1 Vesikari 2011-FIN	4/169	0/44		2.38 [0.13, 43.44]
Subtotal (95% CI)	**2079**	**774**		**1.28 [0.66, 2.50]**
Total events: 27 (RV1), 11 (Placebo)				
Heterogeneity: Chi² = 2.78, df = 6 (P = 0.84); I² =0.0%				
Test for overall effect: Z = 0.72 (P = 0.47)				
2 High-mortality countries (WHO strata D % E)				
RV1 Narang 2009-IND	0/182	0/181		0.0 [0.0, 0.0]
RV1 Steele 2010a-ZAF	4/50	4/50		1.00 [0.26, 3.78]
RV1 Zaman 2009-BGD	8/196	4/98		1.00 [0.31, 3.24]
Subtotal (95% CI)	**428**	**329**		**1.00 [0.41, 2.41]**
Total events: 12 (RV1), 8 (Placebo)				
Heterogeneity: Chi² = 0.0, df = 1 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 0.0 (P = 1.0)				
Total (95% CI)	**2507**	**1103**		**1.17 [0.69, 2.00]**
Total events: 39 (RV1), 19 (Placebo)				
Heterogeneity: Chi² = 2.92, df = 8 (P = 0.94); I² =0.0%				
Test for overall effect: Z = 0.58 (P = 0.56)				
Test for subgroup differences: Chi² = 0.19, df = 1 (P = 0.66), I² =0.0%				



Analysis 1.13. Comparison 1 RV1 versus placebo, Outcome 13 Rotavirus diarrhoea: of any severity (up to 1 year follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 13 Rotavirus diarrhoea: of any severity (up to 1 year follow-up)

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low-mortality countries (WHO strata A % B)					
RV1 Bernstein 1999-USA	2/108	18/107		7.7 %	0.11 [0.03, 0.46]
RV1 Salinas 2005-LA	58/1392	51/454		19.4 %	0.37 [0.26, 0.53]
RV1 Vesikari 2007a-EU	24/2572	94/1302		18.5 %	0.13 [0.08, 0.20]
Subtotal (95% CI)	**4072**	**1863**		**45.6 %**	**0.19 [0.08, 0.47]**
Total events: 84 (RV1), 163 (Placebo)					
Heterogeneity: Tau^2 = 0.49; Chi^2 = 14.80, df = 2 (P = 0.00061); I^2 =86%					
Test for overall effect: Z = 3.60 (P = 0.00031)					
2 High-mortality countries (WHO stratum E)					
RV1 Madhi 2010-MWI (1)	109/1182	85/591		20.4 %	0.64 [0.49, 0.84]
RV1 Madhi 2010-ZAF (2)	91/2116	128/1050		20.5 %	0.35 [0.27, 0.46]
RV1 Steele 2010b-ZAF	13/379	9/96		13.6 %	0.37 [0.16, 0.83]
Subtotal (95% CI)	**3677**	**1737**		**54.4 %**	**0.45 [0.28, 0.73]**
Total events: 213 (RV1), 222 (Placebo)					
Heterogeneity: Tau^2 = 0.13; Chi^2 = 10.33, df = 2 (P = 0.01); I^2 =81%					
Test for overall effect: Z = 3.26 (P = 0.0011)					
Total (95% CI)	**7749**	**3600**		**100.0 %**	**0.31 [0.19, 0.50]**
Total events: 297 (RV1), 385 (Placebo)					
Heterogeneity: Tau^2 = 0.29; Chi^2 = 41.47, df = 5 (P<0.00001); I^2 =88%					
Test for overall effect: Z = 4.67 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 2.73, df = 1 (P = 0.10), I^2 =63%					

(1) Data taken from main paper Supplementary Appendix, Table 5 - total vaccinated cohort in Malawi

(2) Data taken from main paper Supplementary Appendix, Table 5 - total vaccinated cohort in South Africa

Analysis 1.14. Comparison 1 RV1 versus placebo, Outcome 14 Rotavirus diarrhoea: of any severity (up to 2 years follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 14 Rotavirus diarrhoea: of any severity (up to 2 years follow-up)

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low-mortality countries (WHO strata A & B)					
RV1 Bernstein 1999-USA	8/108	33/107		13.7 %	0.24 [0.12, 0.50]
RV1 Phua 2005-SGP	2/1779	4/642		3.6 %	0.18 [0.03, 0.98]
RV1 Salinas 2005-LA	23/332	9/109		13.3 %	0.84 [0.40, 1.76]
RV1 Vesikari 2004b-FIN	13/245	23/123		15.8 %	0.28 [0.15, 0.54]
RV1 Vesikari 2007a-EU	61/2554	110/1294		28.9 %	0.28 [0.21, 0.38]
Subtotal (95% CI)	**5018**	**2275**		**75.3 %**	**0.33 [0.21, 0.50]**
Total events: 107 (RV1), 179 (Placebo)					
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 8.30$, df = 4 (P = 0.08); $I^2 = 52\%$					
Test for overall effect: Z = 5.08 (P < 0.00001)					
2 High-mortality countries (WHO stratum E)					
RV1 Madhi 2010-ZAF (1)	41/843	48/408		24.7 %	0.41 [0.28, 0.62]
Subtotal (95% CI)	**843**	**408**		**24.7 %**	**0.41 [0.28, 0.62]**
Total events: 41 (RV1), 48 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.33 (P = 0.000015)					
Total (95% CI)	**5861**	**2683**		**100.0 %**	**0.35 [0.25, 0.48]**
Total events: 148 (RV1), 227 (Placebo)					
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 9.84$, df = 5 (P = 0.08); $I^2 = 49\%$					
Test for overall effect: Z = 6.22 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 0.61$, df = 1 (P = 0.44), $I^2 = 0.0\%$					

(1) Data from South Africa cohort only

Analysis 1.15. Comparison 1 RV1 versus placebo, Outcome 15 All-cause diarrhoea: all cases (up to 2 months follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 15 All-cause diarrhoea: all cases (up to 2 months follow-up)

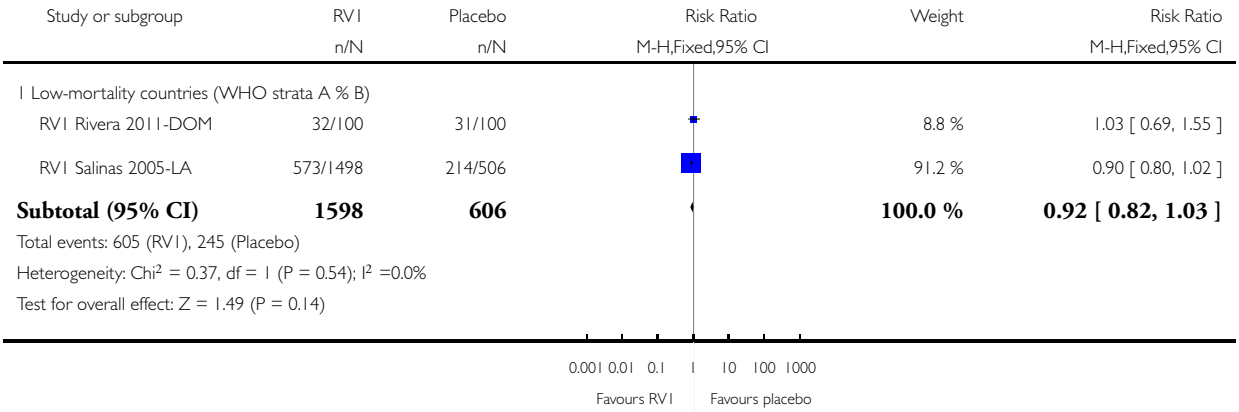
Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-mortality countries (WHO strata A % B)					
RV1 Anh 2011-PHL	29/270	8/66		10.6 %	0.89 [0.42, 1.85]
RV1 Anh 2011-VNM	44/275	11/71		14.4 %	1.03 [0.56, 1.89]
RV1 Kerdpanich 2010-THA	51/392	7/52		10.2 %	0.97 [0.46, 2.02]
RV1 Omenaca 2012-EU	55/670	36/339		39.4 %	0.77 [0.52, 1.15]
RV1 Vesikari 2011-FIN	15/169	5/44		6.5 %	0.78 [0.30, 2.03]
Subtotal (95% CI)	**1776**	**572**		**81.1 %**	**0.86 [0.66, 1.12]**
Total events: 194 (RV1), 67 (Placebo)					
Heterogeneity: Chi^2 = 0.77, df = 4 (P = 0.94); I^2 =0.0%					
Test for overall effect: Z = 1.11 (P = 0.27)					
2 High-mortality countries (WHO stratum E)					
RV1 Steele 2010a-ZAF	24/50	23/50		18.9 %	1.04 [0.69, 1.58]
Subtotal (95% CI)	**50**	**50**		**18.9 %**	**1.04 [0.69, 1.58]**
Total events: 24 (RV1), 23 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.20 (P = 0.84)					
Total (95% CI)	**1826**	**622**		**100.0 %**	**0.89 [0.71, 1.13]**
Total events: 218 (RV1), 90 (Placebo)					
Heterogeneity: Chi^2 = 1.38, df = 5 (P = 0.93); I^2 =0.0%					
Test for overall effect: Z = 0.96 (P = 0.34)					
Test for subgroup differences: Chi^2 = 0.59, df = 1 (P = 0.44), I^2 =0.0%					

Analysis 1.16. Comparison 1 RV1 versus placebo, Outcome 16 All-cause diarrhoea: all cases (up to 1 year follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 16 All-cause diarrhoea: all cases (up to 1 year follow-up)

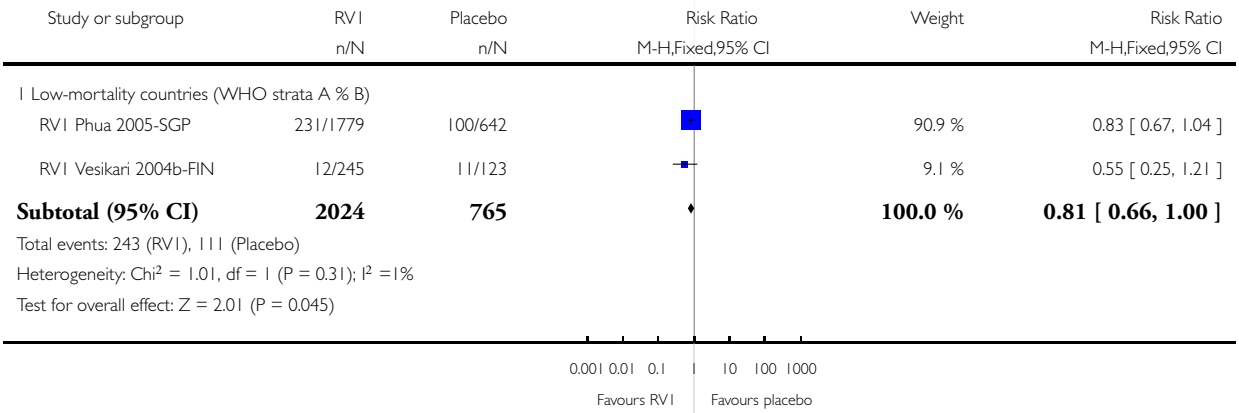


Analysis 1.17. Comparison 1 RV1 versus placebo, Outcome 17 All-cause diarrhoea: all cases (up to 2 years follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 17 All-cause diarrhoea: all cases (up to 2 years follow-up)

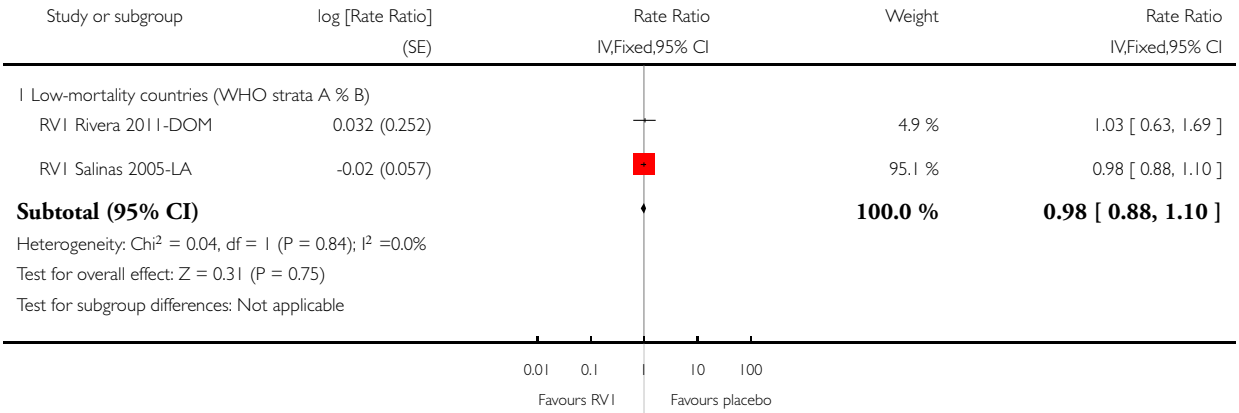


Analysis 1.18. Comparison 1 RV1 versus placebo, Outcome 18 All-cause diarrhoea: all episodes (up to 1 year follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 18 All-cause diarrhoea: all episodes (up to 1 year follow-up)

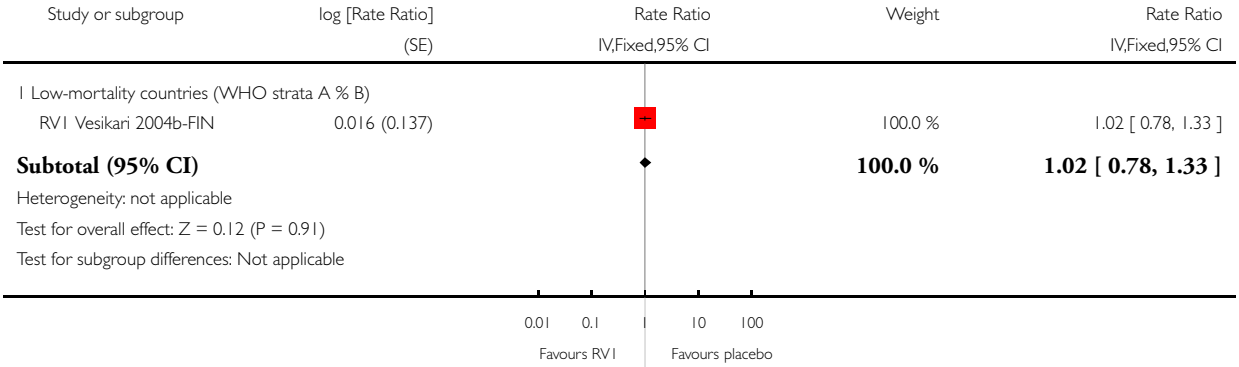


Analysis 1.19. Comparison 1 RV1 versus placebo, Outcome 19 All-cause diarrhoea: all episodes (up to 2 years follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 19 All-cause diarrhoea: all episodes (up to 2 years follow-up)

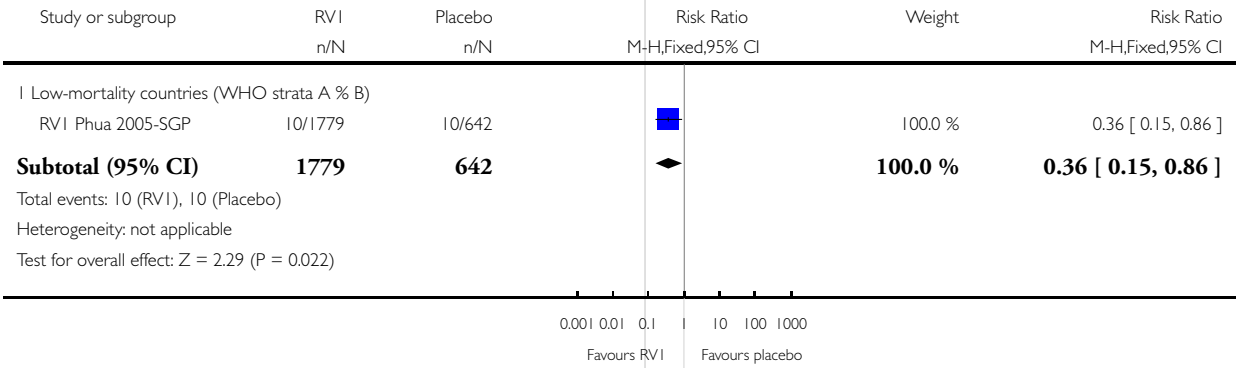


Analysis 1.20. Comparison 1 RV1 versus placebo, Outcome 20 All-cause hospitalizations (up to 2 years follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 20 All-cause hospitalizations (up to 2 years follow-up)



Analysis 1.21. Comparison 1 RV1 versus placebo, Outcome 21 Rotavirus diarrhoea: requiring hospitalization.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 21 Rotavirus diarrhoea: requiring hospitalization

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Up to 1 year follow-up (at least 1 rotavirus season)					
RV1 Bernstein 1999-USA	0/108	2/107		6.0 %	0.20 [0.01, 4.08]
RV1 Madhi 2010-AF (1)	20/3298	19/1641		28.4 %	0.52 [0.28, 0.98]
RV1 Phua 2009-AS	0/5263	13/5256		6.7 %	0.04 [0.00, 0.62]
RV1 Ruiz-Palac 06-LA/EU	9/9009	59/8858		27.2 %	0.15 [0.07, 0.30]
RV1 Salinas 2005-LA	9/1392	14/454		25.1 %	0.21 [0.09, 0.48]
RV1 Vesikari 2007a-EU	0/2572	12/1302		6.7 %	0.02 [0.00, 0.34]
Subtotal (95% CI)	**21642**	**17618**		**100.0 %**	**0.19 [0.08, 0.43]**
Total events: 38 (RV1), 119 (Placebo)					
Heterogeneity: $Tau^2 = 0.51$; $Chi^2 = 13.57$, df = 5 (P = 0.02); $I^2 = 63\%$					
Test for overall effect: Z = 4.02 (P = 0.000059)					
2 Second year follow-up (at least 2 rotavirus seasons)					
RV1 Kawamura 2010-JPN	1/498	2/250		4.2 %	0.25 [0.02, 2.75]
RV1 Phua 2005-SGP	0/1779	1/642		2.4 %	0.12 [0.00, 2.95]
RV1 Phua 2009-AS	3/5263	48/5256		16.3 %	0.06 [0.02, 0.20]
RV1 Ruiz-Palac 06-LA/EU	22/7205	127/7081		64.2 %	0.17 [0.11, 0.27]
RV1 Vesikari 2004b-FIN	1/241	0/120		2.4 %	1.50 [0.06, 36.55]
RV1 Vesikari 2007a-EU	2/2554	13/1294		10.5 %	0.08 [0.02, 0.34]
Subtotal (95% CI)	**17540**	**14643**		**100.0 %**	**0.14 [0.09, 0.23]**
Total events: 29 (RV1), 191 (Placebo)					
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 5.49$, df = 5 (P = 0.36); $I^2 = 9\%$					
Test for overall effect: Z = 7.64 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 0.34$, df = 1 (P = 0.56), $I^2 = 0.0\%$					

(1) Data taken from main paper Supplementary Appendix, Table 3 - total vaccinated cohort.

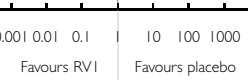
Analysis 1.22. Comparison 1 RV1 versus placebo, Outcome 22 Rotavirus diarrhoea: requiring medical attention.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 22 Rotavirus diarrhoea: requiring medical attention

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Up to 1 year follow-up (at least 1 rotavirus season)					
RV1 Vesikari 2007a-EU	10/2572	62/1302		100.0 %	0.08 [0.04, 0.16]
Subtotal (95% CI)	**2572**	**1302**		**100.0 %**	**0.08 [0.04, 0.16]**
Total events: 10 (RV1), 62 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 7.39 (P < 0.00001)					
2 Second year follow-up (at least 2 rotavirus seasons)					
RV1 Kawamura 2010-JPN	14/498	34/250		32.8 %	0.21 [0.11, 0.38]
RV1 Phua 2005-SGP	0/1779	3/642		3.7 %	0.05 [0.00, 1.00]
RV1 Vesikari 2007a-EU	31/2554	66/1294		63.5 %	0.24 [0.16, 0.36]
Subtotal (95% CI)	**4831**	**2186**		**100.0 %**	**0.22 [0.16, 0.31]**
Total events: 45 (RV1), 103 (Placebo)					
Heterogeneity: Chi^2 = 1.09, df = 2 (P = 0.58); I^2 =0.0%					
Test for overall effect: Z = 8.67 (P < 0.00001)					



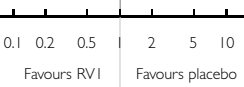
Analysis 1.23. Comparison 1 RV1 versus placebo, Outcome 23 All-cause diarrhoea: cases requiring hospitalization.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 23 All-cause diarrhoea: cases requiring hospitalization

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Up to one year of follow-up (at least 1 rotavirus season)					
RV1 Phua 2009-AS	60/5263	90/5256		55.8 %	0.67 [0.48, 0.92]
RV1 Vesikari 2007a-EU	11/2572	22/1302		44.2 %	0.25 [0.12, 0.52]
Subtotal (95% CI)	**7835**	**6558**		**100.0 %**	**0.43 [0.17, 1.11]**
Total events: 71 (RV1), 112 (Placebo)					
Heterogeneity: Tau^2 = 0.39; Chi^2 = 5.75, df = 1 (P = 0.02); I^2 =83%					
Test for overall effect: Z = 1.74 (P = 0.082)					
2 Second year of follow-up (at least 2 rotavirus seasons)					
RV1 Phua 2009-AS	164/5263	240/5256		59.4 %	0.68 [0.56, 0.83]
RV1 Vesikari 2007a-EU	18/2554	26/1294		40.6 %	0.35 [0.19, 0.64]
Subtotal (95% CI)	**7817**	**6550**		**100.0 %**	**0.52 [0.27, 0.99]**
Total events: 182 (RV1), 266 (Placebo)					
Heterogeneity: Tau^2 = 0.17; Chi^2 = 4.31, df = 1 (P = 0.04); I^2 =77%					
Test for overall effect: Z = 2.00 (P = 0.046)					



Analysis 1.24. Comparison 1 RV1 versus placebo, Outcome 24 All-cause diarrhoea: episodes requiring hospitalization.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 24 All-cause diarrhoea: episodes requiring hospitalization

Study or subgroup	log [Rate Ratio] (SE)	Rate Ratio IV,Fixed,95% CI	Weight	Rate Ratio IV,Fixed,95% CI
1 Up to 1 year of follow-up (at least 1 rotavirus season)				
RV1 Ruiz-Palac 06-LA/EU	-0.546 (0.105)		100.0 %	0.58 [0.47, 0.71]
Subtotal (95% CI)			**100.0 %**	**0.58 [0.47, 0.71]**
Heterogeneity: not applicable				
Test for overall effect: Z = 5.20 (P < 0.00001)				
2 Second year of follow-up (at least 2 rotavirus seasons)				
RV1 Ruiz-Palac 06-LA/EU	-0.636 (0.076)		100.0 %	0.53 [0.46, 0.61]
Subtotal (95% CI)			**100.0 %**	**0.53 [0.46, 0.61]**
Heterogeneity: not applicable				
Test for overall effect: Z = 8.37 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.48, df = 1 (P = 0.49), I^2 =0.0%				

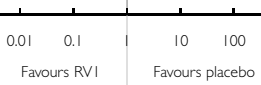
Analysis 1.25. Comparison 1 RV1 versus placebo, Outcome 25 Reactogenicity: fever.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 25 Reactogenicity: fever

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 After dose 1					
RV1 Anh 2011-PHL	239/300	54/75		14.0 %	1.11 [0.95, 1.29]
RV1 Anh 2011-VNM	182/297	44/78		10.4 %	1.09 [0.88, 1.35]
RV1 Bernstein 1998-USA	3/21	6/20		0.6 %	0.48 [0.14, 1.65]
RV1 Bernstein 1999-USA	21/108	5/107		1.0 %	4.16 [1.63, 10.63]
RV1 Dennehy 2005-NA	83/421	21/108		4.1 %	1.01 [0.66, 1.56]
RV1 GSK[021] 2007-PAN	91/177	18/51		4.6 %	1.46 [0.98, 2.17]
RV1 GSK[033] 2007-LA	98/730	15/124		3.1 %	1.11 [0.67, 1.85]
RV1 GSK[041] 2007-KOR	10/100	3/52		0.6 %	1.73 [0.50, 6.03]
RV1 GSK[101555] 2008-PHL	39/100	11/50		2.5 %	1.77 [1.00, 3.16]
RV1 Kerdpanich 2010-THA	68/348	6/52		1.4 %	1.69 [0.77, 3.70]
RV1 Narang 2009-IND	14/182	6/181		1.0 %	2.32 [0.91, 5.90]
RV1 Phua 2005-SGP	497/1811	183/653		14.6 %	0.98 [0.85, 1.13]
RV1 Salinas 2005-LA	1002/1618	346/537		19.3 %	0.96 [0.89, 1.03]
RV1 Steele 2008-ZAF	37/297	21/150		3.2 %	0.89 [0.54, 1.46]
RV1 Steele 2010b-ZAF	62/189	30/96		5.4 %	1.05 [0.73, 1.50]
RV1 Vesikari 2004a-FIN	8/122	3/62		0.5 %	1.36 [0.37, 4.93]
RV1 Vesikari 2004b-FIN	32/265	14/133		2.3 %	1.15 [0.63, 2.07]
RV1 Vesikari 2007a-EU	166/914	91/490		9.6 %	0.98 [0.78, 1.23]
RV1 Vesikari 2011-FIN	9/200	1/50		0.2 %	2.25 [0.29, 17.35]
RV1 Zaman 2009-BGD	16/196	12/98		1.7 %	0.67 [0.33, 1.35]
Subtotal (95% CI)	**8396**	**3167**		**100.0 %**	**1.08 [0.98, 1.18]**
Total events: 2677 (RV1), 890 (Placebo)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 29.53$, df = 19 (P = 0.06); $I^2 = 36\%$					
Test for overall effect: Z = 1.48 (P = 0.14)					
2 After dose 2					
RV1 Anh 2011-PHL	197/296	45/75		10.6 %	1.11 [0.91, 1.36]



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Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
RV1 Anh 2011-VNM	141/286	36/73		7.0 %	1.00 [0.77, 1.30]
RV1 Bernstein 1998-USA	4/21	5/20		0.4 %	0.76 [0.24, 2.44]
RV1 Dennehy 2005-NA	82/394	31/101		4.2 %	0.68 [0.48, 0.96]
RV1 GSK[021] 2007-PAN	57/168	13/47		2.1 %	1.23 [0.74, 2.04]
RV1 GSK[033] 2007-LA	129/683	28/112		4.1 %	0.76 [0.53, 1.08]
RV1 GSK[041] 2007-KOR	8/99	6/52		0.6 %	0.70 [0.26, 1.91]
RV1 GSK[101555] 2008-PHL	29/98	22/50		2.8 %	0.67 [0.43, 1.04]
RV1 Kerdpanich 2010-THA	69/342	12/52		1.9 %	0.87 [0.51, 1.50]
RV1 Narang 2009-IND	18/175	12/173		1.1 %	1.48 [0.74, 2.98]
RV1 Phua 2005-SGP	536/1779	186/642		17.3 %	1.04 [0.90, 1.20]
RV1 Salinas 2005-LA	826/1534	288/522		26.5 %	0.98 [0.89, 1.07]
RV1 Steele 2008-ZAF	34/282	12/143		1.4 %	1.44 [0.77, 2.69]
RV1 Steele 2010b-ZAF	91/369	13/90		1.9 %	1.71 [1.00, 2.91]
RV1 Vesikari 2004a-FIN	5/111	4/60		0.3 %	0.68 [0.19, 2.42]
RV1 Vesikari 2004b-FIN	69/255	31/124		3.9 %	1.08 [0.75, 1.56]
RV1 Vesikari 2007a-EU	244/905	142/486		13.0 %	0.92 [0.77, 1.10]
RV1 Vesikari 2011-FIN	10/196	3/49		0.4 %	0.83 [0.24, 2.91]
RV1 Zaman 2009-BGD	14/195	6/97		0.7 %	1.16 [0.46, 2.93]
Subtotal (95% CI)	**8188**	**2968**		**100.0 %**	**0.98 [0.91, 1.06]**
Total events: 2563 (RV1), 895 (Placebo)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 21.03, df = 18 (P = 0.28); I^2 =14%					
Test for overall effect: Z = 0.45 (P = 0.65)					
3 After dose 3					
RV1 Anh 2011-PHL	182/293	48/75		50.0 %	0.97 [0.80, 1.18]
RV1 Anh 2011-VNM	146/283	40/73		32.8 %	0.94 [0.74, 1.19]
RV1 GSK[021] 2007-PAN	63/168	18/46		10.9 %	0.96 [0.64, 1.44]
RV1 Steele 2010b-ZAF	76/364	13/88		6.3 %	1.41 [0.82, 2.43]
Subtotal (95% CI)	**1108**	**282**		**100.0 %**	**0.98 [0.86, 1.13]**
Total events: 467 (RV1), 119 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.03, df = 3 (P = 0.57); I^2 =0.0%					
Test for overall effect: Z = 0.25 (P = 0.80)					
4 End of follow-up					
RV1 Dennehy 2005-NA	136/421	38/108		2.3 %	0.92 [0.69, 1.23]
RV1 GSK[033] 2007-LA	199/730	33/124		2.0 %	1.02 [0.75, 1.40]

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Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
RV1 GSK[041] 2007-KOR	17/100	8/52		0.3 %	1.11 [0.51, 2.39]
RV1 GSK[101555] 2008-PHL	47/100	24/50		1.6 %	0.98 [0.69, 1.40]
RV1 Kawamura 2010-JPN	62/508	22/257		0.9 %	1.43 [0.90, 2.26]
RV1 Kerdpanich 2010-THA	114/348	16/52		1.0 %	1.06 [0.69, 1.64]
RV1 Narang 2009-IND	29/182	18/181		0.7 %	1.60 [0.92, 2.78]
RV1 Omenaca 2012-EU	54/203	29/100		1.3 %	0.92 [0.63, 1.34]
RV1 Rivera 2011-DOM	32/100	32/100		1.2 %	1.00 [0.67, 1.50]
RV1 Salinas 2005-LA	1238/1618	425/537		75.5 %	0.97 [0.92, 1.02]
RV1 Steele 2008-ZAF	64/297	28/150		1.2 %	1.15 [0.78, 1.72]
RV1 Vesikari 2004a-FIN	8/122	6/62		0.2 %	0.68 [0.25, 1.87]
RV1 Vesikari 2004b-FIN	86/265	33/133		1.7 %	1.31 [0.93, 1.84]
RV1 Vesikari 2007a-EU	310/914	192/490		9.7 %	0.87 [0.75, 1.00]
RV1 Vesikari 2011-FIN	18/200	4/50		0.2 %	1.13 [0.40, 3.18]
RV1 Zaman 2009-BGD	10/196	3/49		0.1 %	0.83 [0.24, 2.91]
Subtotal (95% CI)	**6304**	**2495**		**100.0 %**	**0.97 [0.93, 1.01]**
Total events: 2424 (RV1), 911 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 13.64$, df = 15 (P = 0.55); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.31 (P = 0.19)					

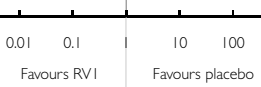
Analysis 1.26. Comparison 1 RV1 versus placebo, Outcome 26 Reactogenicity: diarrhoea.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 26 Reactogenicity: diarrhoea

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 After dose 1					
RV1 Anh 2011-PHL	9/300	6/75		2.8 %	0.38 [0.14, 1.02]
RV1 Anh 2011-VNM	21/297	5/78		3.2 %	1.10 [0.43, 2.83]
RV1 Bernstein 1998-USA	2/21	1/20		0.5 %	1.90 [0.19, 19.40]
RV1 Bernstein 1999-USA	18/108	9/107		4.9 %	1.98 [0.93, 4.21]
RV1 Dennehy 2005-NA	28/421	10/108		5.9 %	0.72 [0.36, 1.43]
RV1 GSK[021] 2007-PAN	33/177	2/51		1.4 %	4.75 [1.18, 19.14]
RV1 GSK[033] 2007-LA	42/730	5/124		3.4 %	1.43 [0.58, 3.54]
RV1 GSK[041] 2007-KOR	5/100	3/52		1.5 %	0.87 [0.22, 3.49]
RV1 GSK[101555] 2008-PHL	6/100	3/50		1.6 %	1.00 [0.26, 3.83]
RV1 Kerdpanich 2010-THA	7/348	1/52		0.7 %	1.05 [0.13, 8.33]
RV1 Narang 2009-IND	11/182	8/181		3.6 %	1.37 [0.56, 3.32]
RV1 Phua 2005-SGP	31/1811	13/653		6.8 %	0.86 [0.45, 1.63]
RV1 Salinas 2005-LA	111/1618	45/537		25.4 %	0.82 [0.59, 1.14]
RV1 Steele 2008-ZAF	29/297	14/150		7.6 %	1.05 [0.57, 1.92]
RV1 Steele 2010b-ZAF	19/189	11/96		5.7 %	0.88 [0.44, 1.77]
RV1 Vesikari 2004a-FIN	11/122	5/62		2.7 %	1.12 [0.41, 3.08]
RV1 Vesikari 2004b-FIN	20/265	7/133		4.0 %	1.43 [0.62, 3.31]
RV1 Vesikari 2007a-EU	68/2613	29/1331		15.2 %	1.19 [0.78, 1.84]
RV1 Vesikari 2011-FIN	10/200	2/50		1.3 %	1.25 [0.28, 5.53]
RV1 Zaman 2009-BGD	5/196	4/98		1.7 %	0.63 [0.17, 2.28]
Subtotal (95% CI)	**10095**	**4008**		**100.0 %**	**1.01 [0.86, 1.20]**
Total events: 486 (RV1), 183 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 17.94$, df = 19 (P = 0.53); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.14 (P = 0.89)					
2 After dose 2					
RV1 Anh 2011-PHL	4/296	0/75		0.5 %	2.30 [0.13, 42.31]



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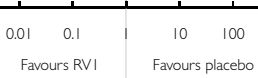
Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
RV1 Anh 2011-VNM	8/286	0/73		0.5 %	4.38 [0.26, 75.08]
RV1 Bernstein 1998-USA	2/21	1/20		0.8 %	1.90 [0.19, 19.40]
RV1 Dennehy 2005-NA	16/394	5/101		4.3 %	0.82 [0.31, 2.19]
RV1 GSK[021] 2007-PAN	21/168	9/47		8.1 %	0.65 [0.32, 1.33]
RV1 GSK[033] 2007-LA	35/683	6/112		5.8 %	0.96 [0.41, 2.22]
RV1 GSK[041] 2007-KOR	5/99	6/52		3.2 %	0.44 [0.14, 1.37]
RV1 GSK[101555] 2008-PHL	6/98	4/50		2.8 %	0.77 [0.23, 2.59]
RV1 Kerdpanich 2010-THA	15/342	1/52		1.0 %	2.28 [0.31, 16.90]
RV1 Narang 2009-IND	5/175	8/173		3.4 %	0.62 [0.21, 1.85]
RV1 Phua 2005-SGP	36/1779	7/642		6.3 %	1.86 [0.83, 4.15]
RV1 Salinas 2005-LA	116/1534	46/522		38.3 %	0.86 [0.62, 1.19]
RV1 Steele 2008-ZAF	22/282	9/143		7.3 %	1.24 [0.59, 2.62]
RV1 Steele 2010b-ZAF	33/369	7/90		6.7 %	1.15 [0.53, 2.51]
RV1 Vesikari 2004a-FIN	3/111	2/60		1.3 %	0.81 [0.14, 4.72]
RV1 Vesikari 2004b-FIN	11/255	2/124		1.8 %	2.67 [0.60, 11.88]
RV1 Vesikari 2007a-EU	15/905	9/486		6.1 %	0.90 [0.39, 2.03]
RV1 Vesikari 2011-FIN	5/196	2/49		1.6 %	0.63 [0.12, 3.13]
RV1 Zaman 2009-BGD	0/195	1/97		0.4 %	0.17 [0.01, 4.05]
Subtotal (95% CI)	**8188**	**2968**		**100.0 %**	**0.93 [0.76, 1.14]**
Total events: 358 (RV1), 125 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 13.38$, df = 18 (P = 0.77); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.69 (P = 0.49)					
3 After dose 3					
RV1 Anh 2011-PHL	3/293	1/75		8.3 %	0.77 [0.08, 7.28]
RV1 Anh 2011-VNM	3/283	4/73		17.2 %	0.19 [0.04, 0.85]
RV1 GSK[021] 2007-PAN	18/168	4/46		29.3 %	1.23 [0.44, 3.46]
RV1 Steele 2010b-ZAF	28/364	9/88		45.2 %	0.75 [0.37, 1.54]
Subtotal (95% CI)	**1108**	**282**		**100.0 %**	**0.69 [0.35, 1.36]**
Total events: 52 (RV1), 18 (Placebo)					
Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 4.11$, df = 3 (P = 0.25); $I^2 = 27\%$					
Test for overall effect: Z = 1.07 (P = 0.28)					
4 End of follow-up					
RV1 Dennehy 2005-NA	41/421	14/108		6.6 %	0.75 [0.43, 1.33]
RV1 GSK[033] 2007-LA	74/730	11/124		5.9 %	1.14 [0.62, 2.09]



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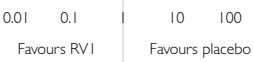
Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
RV1 GSK[041] 2007-KOR	9/100	9/52		2.9 %	0.52 [0.22, 1.23]
RV1 GSK[101555] 2008-PHL	11/100	7/50		2.7 %	0.79 [0.32, 1.90]
RV1 Kawamura 2010-JPN	43/508	14/257		6.3 %	1.55 [0.87, 2.79]
RV1 Kerdpanich 2010-THA	20/348	2/52		1.1 %	1.49 [0.36, 6.21]
RV1 Narang 2009-IND	16/182	15/181		4.7 %	1.06 [0.54, 2.08]
RV1 Omenaca 2012-EU	9/203	5/100		1.9 %	0.89 [0.31, 2.58]
RV1 Salinas 2005-LA	206/1618	85/537		39.6 %	0.80 [0.64, 1.02]
RV1 Steele 2008-ZAF	45/297	20/150		9.0 %	1.14 [0.70, 1.85]
RV1 Vesikari 2004a-FIN	11/122	7/62		2.7 %	0.80 [0.33, 1.96]
RV1 Vesikari 2004b-FIN	30/265	8/133		3.8 %	1.88 [0.89, 3.99]
RV1 Vesikari 2007a-EU	44/2613	25/1331		9.1 %	0.90 [0.55, 1.46]
RV1 Vesikari 2011-FIN	7/193	2/47		0.9 %	0.85 [0.18, 3.97]
RV1 Zaman 2009-BGD	11/196	8/98		2.8 %	0.69 [0.29, 1.65]
Subtotal (95% CI)	**7896**	**3282**		**100.0 %**	**0.92 [0.80, 1.07]**
Total events: 577 (RV1), 232 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 12.60, df = 14 (P = 0.56); I^2 =0.0%					
Test for overall effect: Z = 1.10 (P = 0.27)					



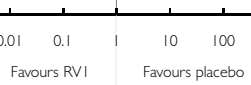
Analysis 1.27. Comparison 1 RV1 versus placebo, Outcome 27 Reactogenicity: vomiting.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 27 Reactogenicity: vomiting

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 After dose 1					
RV1 Anh 2011-PHL	56/300	5/75		1.3 %	2.80 [1.16, 6.74]
RV1 Anh 2011-VNM	39/297	6/78		1.5 %	1.71 [0.75, 3.89]
RV1 Bernstein 1998-USA	4/21	2/20		0.4 %	1.90 [0.39, 9.28]
RV1 Bernstein 1999-USA	16/108	10/107		1.8 %	1.59 [0.75, 3.33]
RV1 Dennehy 2005-NA	56/421	19/108		4.4 %	0.76 [0.47, 1.22]
RV1 GSK[021] 2007-PAN	36/177	10/51		2.5 %	1.04 [0.55, 1.94]
RV1 GSK[033] 2007-LA	115/730	22/124		5.8 %	0.89 [0.59, 1.34]
RV1 GSK[041] 2007-KOR	18/100	11/52		2.2 %	0.85 [0.43, 1.66]
RV1 GSK[101555] 2008-PHL	15/100	9/50		1.7 %	0.83 [0.39, 1.77]
RV1 Kerdpanich 2010-THA	103/348	13/52		4.0 %	1.18 [0.72, 1.95]
RV1 Narang 2009-IND	24/182	24/181		3.6 %	0.99 [0.59, 1.68]
RV1 Phua 2005-SGP	102/1811	39/653		7.7 %	0.94 [0.66, 1.35]
RV1 Salinas 2005-LA	285/1618	89/537		21.0 %	1.06 [0.86, 1.32]
RV1 Steele 2008-ZAF	55/297	21/150		4.6 %	1.32 [0.83, 2.10]
RV1 Steele 2010b-ZAF	24/189	14/96		2.6 %	0.87 [0.47, 1.61]
RV1 Vesikari 2004a-FIN	20/122	14/62		2.7 %	0.73 [0.39, 1.34]
RV1 Vesikari 2004b-FIN	23/265	6/133		1.3 %	1.92 [0.80, 4.61]
RV1 Vesikari 2007a-EU	290/2613	141/1331		27.4 %	1.05 [0.87, 1.27]
RV1 Vesikari 2011-FIN	39/200	7/50		1.8 %	1.39 [0.66, 2.93]
RV1 Zaman 2009-BGD	22/196	8/98		1.7 %	1.38 [0.64, 2.98]
Subtotal (95% CI)	**10095**	**4008**		**100.0 %**	**1.06 [0.96, 1.17]**
Total events: 1342 (RV1), 470 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 17.35$, df = 19 (P = 0.57); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.08 (P = 0.28)					
2 After dose 2					
RV1 Anh 2011-PHL	32/296	5/75		2.9 %	1.62 [0.65, 4.02]



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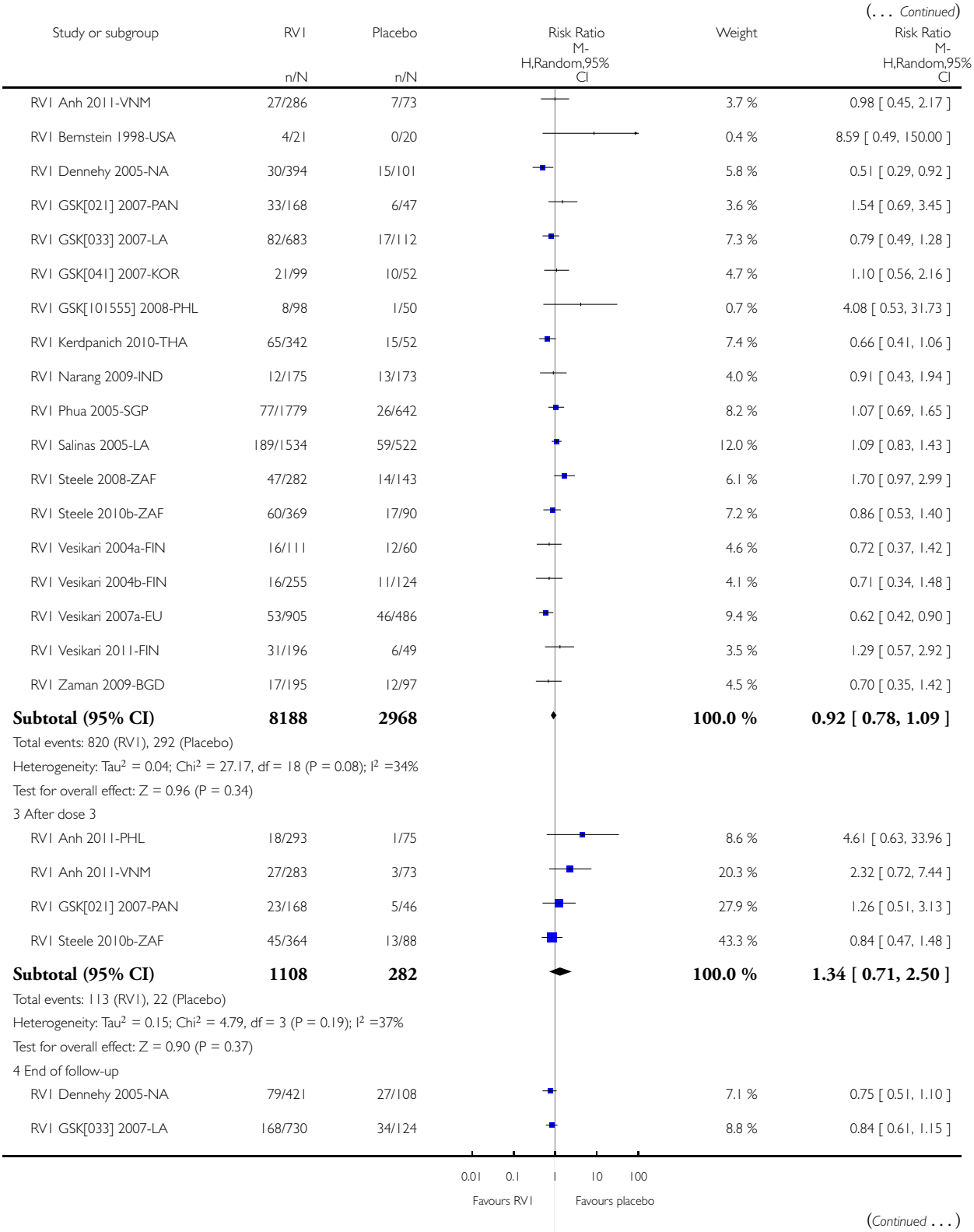

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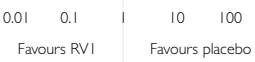
Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
RV1 GSK[041] 2007-KOR	27/100	17/52		4.8 %	0.83 [0.50, 1.37]
RV1 GSK[101555] 2008-PHL	21/100	9/50		2.8 %	1.17 [0.58, 2.36]
RV1 Kawamura 2010-JPN	74/508	36/257		7.4 %	1.04 [0.72, 1.50]
RV1 Kerdpanich 2010-THA	131/348	20/52		7.4 %	0.98 [0.68, 1.42]
RV1 Narang 2009-IND	29/182	32/181		5.6 %	0.90 [0.57, 1.43]
RV1 Omenaca 2012-EU	52/203	27/100		6.7 %	0.95 [0.64, 1.41]
RV1 Salinas 2005-LA	403/1618	129/537		14.1 %	1.04 [0.87, 1.23]
RV1 Steele 2008-ZAF	82/297	31/150		7.5 %	1.34 [0.93, 1.92]
RV1 Vesikari 2004a-FIN	30/122	21/62		5.4 %	0.73 [0.46, 1.16]
RV1 Vesikari 2004b-FIN	34/265	14/133		3.8 %	1.22 [0.68, 2.19]
RV1 Vesikari 2007a-EU	154/2613	126/1331		11.9 %	0.62 [0.50, 0.78]
RV1 Vesikari 2011-FIN	34/193	6/47		2.2 %	1.38 [0.62, 3.09]
RV1 Zaman 2009-BGD	36/196	16/98		4.4 %	1.13 [0.66, 1.92]
Subtotal (95% CI)	**7896**	**3282**		**100.0 %**	**0.93 [0.82, 1.05]**
Total events: 1354 (RV1), 545 (Placebo)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 23.32$, df = 14 (P = 0.06); $I^2 = 40\%$					
Test for overall effect: Z = 1.15 (P = 0.25)					



Analysis 1.28. Comparison 1 RV1 versus placebo, Outcome 28 Adverse events requiring discontinuation (end of follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 28 Adverse events requiring discontinuation (end of follow-up)

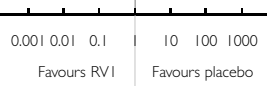
Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
RV1 Anh 2011-PHL	1/300	0/75		0.76 [0.03, 18.41]
RV1 Anh 2011-VNM	1/297	0/78		0.80 [0.03, 19.34]
RV1 Bernstein 1998-USA	1/21	0/20		2.86 [0.12, 66.44]
RV1 Dennehy 2005-NA	5/421	1/108		1.28 [0.15, 10.86]
RV1 GSK[021] 2007-PAN	0/177	1/51		0.10 [0.00, 2.35]
RV1 GSK[024] 2008-LA	12/4376	3/2192		2.00 [0.57, 7.09]
RV1 GSK[033] 2007-LA	4/730	0/122		1.51 [0.08, 27.95]
RV1 GSK[041] 2007-KOR	0/103	0/52		0.0 [0.0, 0.0]
RV1 GSK[101555] 2008-PHL	0/100	0/50		0.0 [0.0, 0.0]
RV1 Kawamura 2010-JPN	1/508	1/257		0.51 [0.03, 8.06]
RV1 Kerdpanich 2010-THA	0/348	0/52		0.0 [0.0, 0.0]
RV1 Narang 2009-IND	1/182	0/181		2.98 [0.12, 72.76]
RV1 Phua 2009-AS	7/5263	12/5256		0.58 [0.23, 1.48]
RV1 Ruiz-Palac 06-LA/EU	118/31673	104/31552		1.13 [0.87, 1.47]
RV1 Steele 2008-ZAF	4/300	4/150		0.50 [0.13, 1.97]
RV1 Steele 2010b-ZAF	4/379	1/95		1.00 [0.11, 8.87]
RV1 Vesikari 2004a-FIN	5/128	0/64		5.54 [0.31, 98.71]
RV1 Vesikari 2004b-FIN	6/270	2/135		1.50 [0.31, 7.33]
RV1 Vesikari 2007a-EU	7/2646	6/1348		0.59 [0.20, 1.77]
RV1 Vesikari 2011-FIN	1/200	0/50		0.76 [0.03, 18.41]
RV1 Zaman 2009-BGD	1/196	0/98		1.51 [0.06, 36.67]
Total (95% CI)	**48618**	**41986**		**1.07 [0.86, 1.34]**

Total events: 179 (RV1), 135 (Placebo)

Heterogeneity: $Chi^2 = 9.97$, df = 17 (P = 0.91); $I^2 = 0.0\%$

Test for overall effect: Z = 0.62 (P = 0.53)

Test for subgroup differences: Not applicable



Analysis 1.29. Comparison 1 RV1 versus placebo, Outcome 29 Immunogenicity: rotavirus vaccine shedding (end of follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 29 Immunogenicity: rotavirus vaccine shedding (end of follow-up)

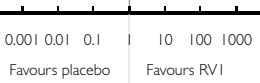
Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
RV1 Bernstein 1998-USA	17/20	0/20		5.0 %	35.00 [2.25, 544.92]
RV1 Bernstein 1999-USA	75/100	1/107		6.7 %	80.25 [11.37, 566.35]
RV1 Dennehy 2005-NA	184/328	2/78		8.3 %	21.88 [5.55, 86.22]
RV1 GSK[021] 2007-PAN	35/88	0/26		4.9 %	21.54 [1.37, 339.58]
RV1 GSK[033] 2007-LA	14/26	1/6		7.1 %	3.23 [0.52, 20.02]
RV1 GSK[101555] 2008-PHL	50/86	7/40		10.0 %	3.32 [1.66, 6.67]
RV1 Kerdpanich 2010-THA	198/337	1/51		6.8 %	29.96 [4.29, 209.08]
RV1 Salinas 2005-LA	44/267	1/93		6.7 %	15.33 [2.14, 109.68]
RV1 Steele 2008-ZAF	19/76	0/39		4.9 %	20.26 [1.26, 326.90]
RV1 Steele 2010a-ZAF	15/23	7/22		10.0 %	2.05 [1.04, 4.05]
RV1 Steele 2010b-ZAF	41/109	0/23		5.0 %	18.11 [1.15, 284.20]
RV1 Vesikari 2004a-FIN	9/122	0/62		4.8 %	9.73 [0.58, 164.51]
RV1 Vesikari 2011-FIN	101/193	0/46		4.9 %	49.18 [3.11, 777.27]
RV1 Ward 2006-USA	74/75	0/36		5.0 %	72.54 [4.62, 1138.35]
RV1 Zaman 2009-BGD	45/71	7/36		10.0 %	3.26 [1.64, 6.49]
Total (95% CI)	**1921**	**685**		**100.0 %**	**12.07 [5.23, 27.85]**

Total events: 921 (RV1), 27 (Placebo)

Heterogeneity: Tau^2 = 1.70; Chi^2 = 61.54, df = 14 (P<0.00001); I^2 =77%

Test for overall effect: Z = 5.84 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.30. Comparison 1 RV1 versus placebo, Outcome 30 Immunogenicity: seroconversion.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 30 Immunogenicity: seroconversion

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 After dose 1					
RV1 Bernstein 1998-USA	16/20	0/21		6.9 %	34.57 [2.21, 540.36]
RV1 GSK[021] 2007-PAN	59/140	2/38		14.3 %	8.01 [2.05, 31.29]
RV1 GSK[101555] 2008-PHL	34/77	4/39		17.3 %	4.31 [1.65, 11.26]
RV1 Phua 2005-SGP	357/442	3/155		16.1 %	41.73 [13.60, 128.09]
RV1 Salinas 2005-LA	157/405	1/139		10.5 %	53.88 [7.61, 381.29]
RV1 Steele 2008-ZAF	72/201	2/110		14.2 %	19.70 [4.93, 78.76]
RV1 Steele 2010b-ZAF	30/283	0/65		6.8 %	14.18 [0.88, 228.86]
RV1 Vesikari 2004a-FIN	85/122	0/62		6.9 %	87.59 [5.53, 1388.36]
RV1 Vesikari 2011-FIN	130/176	0/42		6.9 %	63.41 [4.02, 998.86]
Subtotal (95% CI)	**1866**	**671**		**100.0 %**	**20.39 [8.48, 49.01]**
Total events: 940 (RV1), 12 (Placebo)					
Heterogeneity: $Tau^2 = 0.91$; $Chi^2 = 18.72$, df = 8 (P = 0.02); $I^2 = 57\%$					
Test for overall effect: Z = 6.74 (P < 0.00001)					
2 After dose 2					
RV1 Bernstein 1998-USA	19/21	0/20		2.0 %	37.23 [2.40, 578.09]
RV1 Bernstein 1999-USA	98/107	0/106		2.0 %	195.18 [12.28, 3102.13]
RV1 Dennehy 2005-NA	197/271	4/63		5.7 %	11.45 [4.42, 29.64]
RV1 GSK[021] 2007-PAN	96/139	2/37		4.5 %	12.78 [3.30, 49.41]
RV1 GSK[024] 2008-LA	108/176	14/89		6.9 %	3.90 [2.38, 6.40]
RV1 GSK[033] 2007-LA	355/494	9/91		6.6 %	7.27 [3.90, 13.54]
RV1 GSK[041] 2007-KOR	32/48	1/24		3.2 %	16.00 [2.32, 110.13]
RV1 GSK[101555] 2008-PHL	60/76	6/39		6.3 %	5.13 [2.44, 10.81]
RV1 Kawamura 2010-JPN	29/34	1/20		3.2 %	17.06 [2.51, 115.83]
RV1 Kerdpanich 2010-THA	290/352	0/51		2.0 %	85.59 [5.42, 1350.73]
RV1 Narang 2009-IND	67/115	7/112		6.3 %	9.32 [4.48, 19.42]
RV1 Omenaca 2012-EU	126/147	13/81		6.9 %	5.34 [3.23, 8.83]

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Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
RV1 Phua 2005-SGP	379/445	4/151		5.6 %	32.15 [12.22, 84.62]
RV1 Rivera 2011-DOM	50/80	17/80		7.0 %	2.94 [1.87, 4.63]
RV1 Salinas 2005-LA	246/391	5/132		5.9 %	16.61 [7.01, 39.37]
RV1 Steele 2008-ZAF	86/182	5/106		5.9 %	10.02 [4.20, 23.89]
RV1 Vesikari 2004a-FIN	106/122	0/62		2.0 %	109.10 [6.89, 1726.59]
RV1 Vesikari 2004b-FIN	168/209	0/112		2.0 %	181.34 [11.40, 2883.75]
RV1 Vesikari 2007a-EU	687/794	28/422		7.2 %	13.04 [9.11, 18.67]
RV1 Vesikari 2011-FIN	144/166	0/44		2.0 %	77.87 [4.94, 1226.73]
RV1 Zaman 2009-BGD	83/135	13/70		6.9 %	3.31 [1.99, 5.50]
Subtotal (95% CI)	**4504**	**1912**		**100.0 %**	**11.04 [7.03, 17.34]**
Total events: 3426 (RV1), 129 (Placebo)					
Heterogeneity: $Tau^2 = 0.70$; $Chi^2 = 110.09$, df = 20 ($P<0.00001$); $I^2 = 82\%$					
Test for overall effect: $Z = 10.43$ ($P < 0.00001$)					
3 After dose 3					
RV1 Anh 2011-PHL	155/240	3/52		23.8 %	11.19 [3.72, 33.71]
RV1 Anh 2011-VNM	178/247	10/65		41.2 %	4.68 [2.63, 8.33]
RV1 GSK[021] 2007-PAN	111/130	3/37		24.2 %	10.53 [3.55, 31.23]
RV1 Steele 2010b-ZAF	117/264	1/59		10.7 %	26.15 [3.73, 183.41]
Subtotal (95% CI)	**881**	**213**		**100.0 %**	**8.43 [4.16, 17.11]**
Total events: 561 (RV1), 17 (Placebo)					
Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 5.49$, df = 3 ($P = 0.14$); $I^2 = 45\%$					
Test for overall effect: $Z = 5.91$ ($P < 0.00001$)					

Analysis 1.31. Comparison 1 RV1 versus placebo, Outcome 31 Drop outs before the end of the trial.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 31 Drop outs before the end of the trial

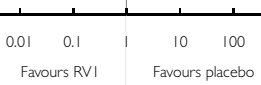
Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RV1 Anh 2011-PHL	8/300	1/75		0.3 %	2.00 [0.25, 15.75]
RV1 Anh 2011-VNM	16/297	5/78		1.4 %	0.84 [0.32, 2.22]
RV1 GSK[021] 2007-PAN	19/177	6/51		1.6 %	0.91 [0.38, 2.16]
RV1 GSK[024] 2008-LA	142/4376	77/2192		17.5 %	0.92 [0.70, 1.21]
RV1 GSK[033] 2007-LA	47/730	12/124		3.5 %	0.67 [0.36, 1.22]
RV1 GSK[041] 2007-KOR	4/103	0/52		0.1 %	4.59 [0.25, 83.60]
RV1 GSK[101555] 2008-PHL	5/100	0/50		0.1 %	5.55 [0.31, 98.50]
RV1 Kawamura 2010-JPN	32/508	16/257		3.6 %	1.01 [0.57, 1.81]
RV1 Kerdpanich 2010-THA	9/348	0/52		0.1 %	2.89 [0.17, 48.85]
RV1 Madhi 2010-AF	324/3298	198/1641		45.2 %	0.81 [0.69, 0.96]
RV1 Narang 2009-IND	9/182	10/181		1.7 %	0.90 [0.37, 2.15]
RV1 Omenaca 2012-EU	15/670	6/339		1.4 %	1.26 [0.50, 3.23]
RV1 Phua 2005-SGP	69/1811	25/653		6.3 %	1.00 [0.64, 1.56]
RV1 Rivera 2011-DOM	5/100	5/100		0.9 %	1.00 [0.30, 3.35]
RV1 Steele 2008-ZAF	30/300	14/150		3.2 %	1.07 [0.59, 1.96]
RV1 Steele 2010a-ZAF	14/50	12/50		2.1 %	1.17 [0.60, 2.27]
RV1 Steele 2010b-ZAF	42/379	13/96		3.5 %	0.82 [0.46, 1.46]
RV1 Vesikari 2004a-FIN	12/128	2/64		0.5 %	3.00 [0.69, 13.00]
RV1 Vesikari 2004b-FIN	21/270	12/135		2.7 %	0.88 [0.44, 1.72]
RV1 Vesikari 2007a-EU	33/2646	17/1348		3.8 %	0.99 [0.55, 1.77]
RV1 Vesikari 2011-FIN	5/200	1/50		0.3 %	1.25 [0.15, 10.46]
RV1 Zaman 2009-BGD	3/196	1/98		0.2 %	1.50 [0.16, 14.23]
Total (95% CI)	**17169**	**7836**		**100.0 %**	**0.91 [0.81, 1.02]**

Total events: 864 (RV1), 433 (Placebo)

Heterogeneity: Chi^2 = 11.33, df = 21 (P = 0.96); I^2 =0.0%

Test for overall effect: Z = 1.65 (P = 0.099)

Test for subgroup differences: Not applicable



Analysis 1.32. Comparison 1 RV1 versus placebo, Outcome 32 Subgroup analysis: rotavirus diarrhoea of any severity (by G type).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 32 Subgroup analysis: rotavirus diarrhoea of any severity (by G type)

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 G1					
RV1 Kawamura 2010-JPN	5/498	19/250		20.2 %	0.13 [0.05, 0.35]
RV1 Ruiz-Palac 06-LA/EU	3/9009	36/8858		16.3 %	0.08 [0.03, 0.27]
RV1 Salinas 2005-LA	25/1392	30/454		31.5 %	0.27 [0.16, 0.46]
RV1 Vesikari 2007a-EU	18/2572	89/1302		32.0 %	0.10 [0.06, 0.17]
Subtotal (95% CI)	**13471**	**10864**		**100.0 %**	**0.14 [0.08, 0.26]**
Total events: 51 (RV1), 174 (Placebo)					
Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 8.72$, df = 3 (P = 0.03); I^2 =66%					
Test for overall effect: Z = 6.23 (P < 0.00001)					
2 G2					
RV1 Ruiz-Palac 06-LA/EU	6/9009	10/8858		30.6 %	0.59 [0.21, 1.62]
RV1 Salinas 2005-LA	1/1392	3/454		6.1 %	0.11 [0.01, 1.04]
RV1 Vesikari 2007a-EU	14/2572	17/1302		63.2 %	0.42 [0.21, 0.84]
Subtotal (95% CI)	**12973**	**10614**		**100.0 %**	**0.43 [0.24, 0.75]**
Total events: 21 (RV1), 30 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.80$, df = 2 (P = 0.41); I^2 =0.0%					
Test for overall effect: Z = 2.98 (P = 0.0029)					
3 G3					
RV1 Salinas 2005-LA	1/1392	2/454		22.4 %	0.16 [0.01, 1.79]
RV1 Vesikari 2007a-EU	3/2572	10/1302		77.6 %	0.15 [0.04, 0.55]
Subtotal (95% CI)	**3964**	**1756**		**100.0 %**	**0.15 [0.05, 0.48]**
Total events: 4 (RV1), 12 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.96); I^2 =0.0%					
Test for overall effect: Z = 3.23 (P = 0.0013)					
4 G4					
RV1 Salinas 2005-LA	1/1392	0/454		10.5 %	0.98 [0.04, 24.01]
RV1 Vesikari 2007a-EU	6/2572	18/1302		89.5 %	0.17 [0.07, 0.42]
Subtotal (95% CI)	**3964**	**1756**		**100.0 %**	**0.20 [0.07, 0.59]**

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Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 7 (RV1), 18 (Placebo)					
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 1.07$, df = 1 (P = 0.30); $I^2 = 7\%$					
Test for overall effect: Z = 2.95 (P = 0.0032)					
5 G9					
RV1 Salinas 2005-LA	29/1392	15/454		45.9 %	0.63 [0.34, 1.17]
RV1 Vesikari 2007a-EU	38/2572	71/1302		54.1 %	0.27 [0.18, 0.40]
Subtotal (95% CI)	**3964**	**1756**		**100.0 %**	**0.40 [0.17, 0.91]**
Total events: 67 (RV1), 86 (Placebo)					
Heterogeneity: $Tau^2 = 0.29$; $Chi^2 = 5.20$, df = 1 (P = 0.02); $I^2 = 81\%$					
Test for overall effect: Z = 2.18 (P = 0.029)					
Test for subgroup differences: $Chi^2 = 8.84$, df = 4 (P = 0.07), $I^2 = 55\%$					

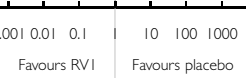
Analysis 1.33. Comparison 1 RV1 versus placebo, Outcome 33 Subgroup analysis: severe cases of rotavirus diarrhoea (by G type).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 33 Subgroup analysis: severe cases of rotavirus diarrhoea (by G type)

Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 G1					
RV1 GSK[024] 2008-LA	6/4211	16/2099		23.4 %	0.19 [0.07, 0.48]
RV1 Kawamura 2010-JPN	1/498	6/250		7.5 %	0.08 [0.01, 0.69]
RV1 Madhi 2010-AF	17/2794	23/1443		33.1 %	0.38 [0.20, 0.71]
RV1 Phua 2009-AS	0/5263	21/5256		4.5 %	0.02 [0.00, 0.38]
RV1 Ruiz-Palac 06-LA/EU	10/7205	55/7081		31.4 %	0.18 [0.09, 0.35]
Subtotal (95% CI)	**19971**	**16129**		**100.0 %**	**0.20 [0.11, 0.37]**
Total events: 34 (RV1), 121 (Placebo)					
Heterogeneity: Tau^2 = 0.21; Chi^2 = 7.36, df = 4 (P = 0.12); I^2 =46%					
Test for overall effect: Z = 5.04 (P < 0.00001)					
2 G2					
RV1 GSK[024] 2008-LA	1/4211	2/2099		14.3 %	0.25 [0.02, 2.75]
RV1 Phua 2005-SGP	0/1779	1/642		8.0 %	0.12 [0.00, 2.95]
RV1 Phua 2009-AS	0/5263	2/5256		8.9 %	0.20 [0.01, 4.16]
RV1 Ruiz-Palac 06-LA/EU	5/9009	9/8858		68.8 %	0.55 [0.18, 1.63]
Subtotal (95% CI)	**20262**	**16855**		**100.0 %**	**0.40 [0.16, 0.98]**
Total events: 6 (RV1), 14 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.20, df = 3 (P = 0.75); I^2 =0.0%					
Test for overall effect: Z = 2.01 (P = 0.045)					
3 G3					
RV1 Phua 2005-SGP	2/1779	0/642		44.6 %	1.81 [0.09, 37.57]
RV1 Phua 2009-AS	1/5263	18/5256		55.4 %	0.06 [0.01, 0.42]
Subtotal (95% CI)	**7042**	**5898**		**100.0 %**	**0.26 [0.01, 8.16]**
Total events: 3 (RV1), 18 (Placebo)					
Heterogeneity: Tau^2 = 4.50; Chi^2 = 3.60, df = 1 (P = 0.06); I^2 =72%					
Test for overall effect: Z = 0.76 (P = 0.45)					
4 G4					
RV1 Phua 2005-SGP	0/1779	1/642		100.0 %	0.12 [0.00, 2.95]
Subtotal (95% CI)	**1779**	**642**		**100.0 %**	**0.12 [0.00, 2.95]**



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Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 0 (RV1), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.30 (P = 0.19)					
5 G9					
RV1 GSK[024] 2008-LA	7/4211	19/2099		79.3 %	0.18 [0.08, 0.44]
RV1 Phua 2005-SGP	0/1779	2/642		6.4 %	0.07 [0.00, 1.50]
RV1 Phua 2009-AS	1/5263	12/5256		14.3 %	0.08 [0.01, 0.64]
Subtotal (95% CI)	**11253**	**7997**		**100.0 %**	**0.15 [0.07, 0.33]**
Total events: 8 (RV1), 33 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.78, df = 2 (P = 0.68); I^2 =0.0%					
Test for overall effect: Z = 4.75 (P < 0.00001)					

Analysis 1.34. Comparison 1 RV1 versus placebo, Outcome 34 Subgroup analysis: rotavirus diarrhoea in malnourished children.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 34 Subgroup analysis: rotavirus diarrhoea in malnourished children

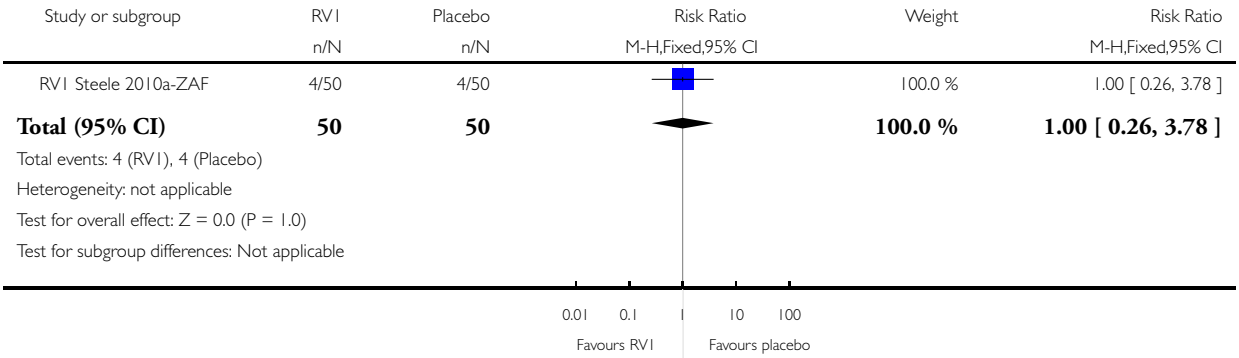
Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Up to 1 year of follow-up (at least 1 rotavirus season)					
RV1 Salinas 2005-LA	14/211	13/76		100.0 %	0.39 [0.19, 0.79]
Total (95% CI)	**211**	**76**		**100.0 %**	**0.39 [0.19, 0.79]**
Total events: 14 (RV1), 13 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.62 (P = 0.0087)					
Test for subgroup differences: Not applicable					

Analysis 1.35. Comparison 1 RV1 versus placebo, Outcome 35 Subgroup analysis: rotavirus diarrhoea in HIV-infected children.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 35 Subgroup analysis: rotavirus diarrhoea in HIV-infected children

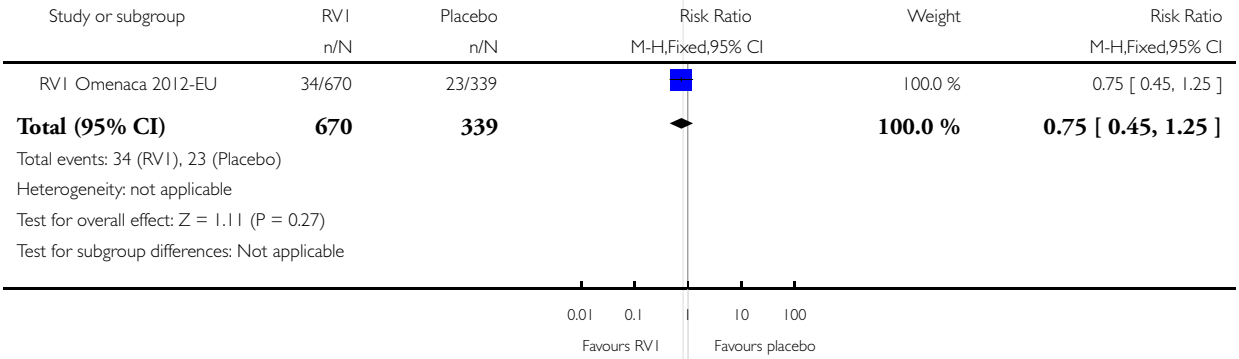


Analysis 1.36. Comparison 1 RV1 versus placebo, Outcome 36 Subgroup analysis: serious adverse events in premature babies.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 36 Subgroup analysis: serious adverse events in premature babies



Analysis 1.37. Comparison 1 RV1 versus placebo, Outcome 37 Subgroup analysis: severe rotavirus diarrhoea in breast fed and formula fed infants.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 37 Subgroup analysis: severe rotavirus diarrhoea in breast fed and formula fed infants

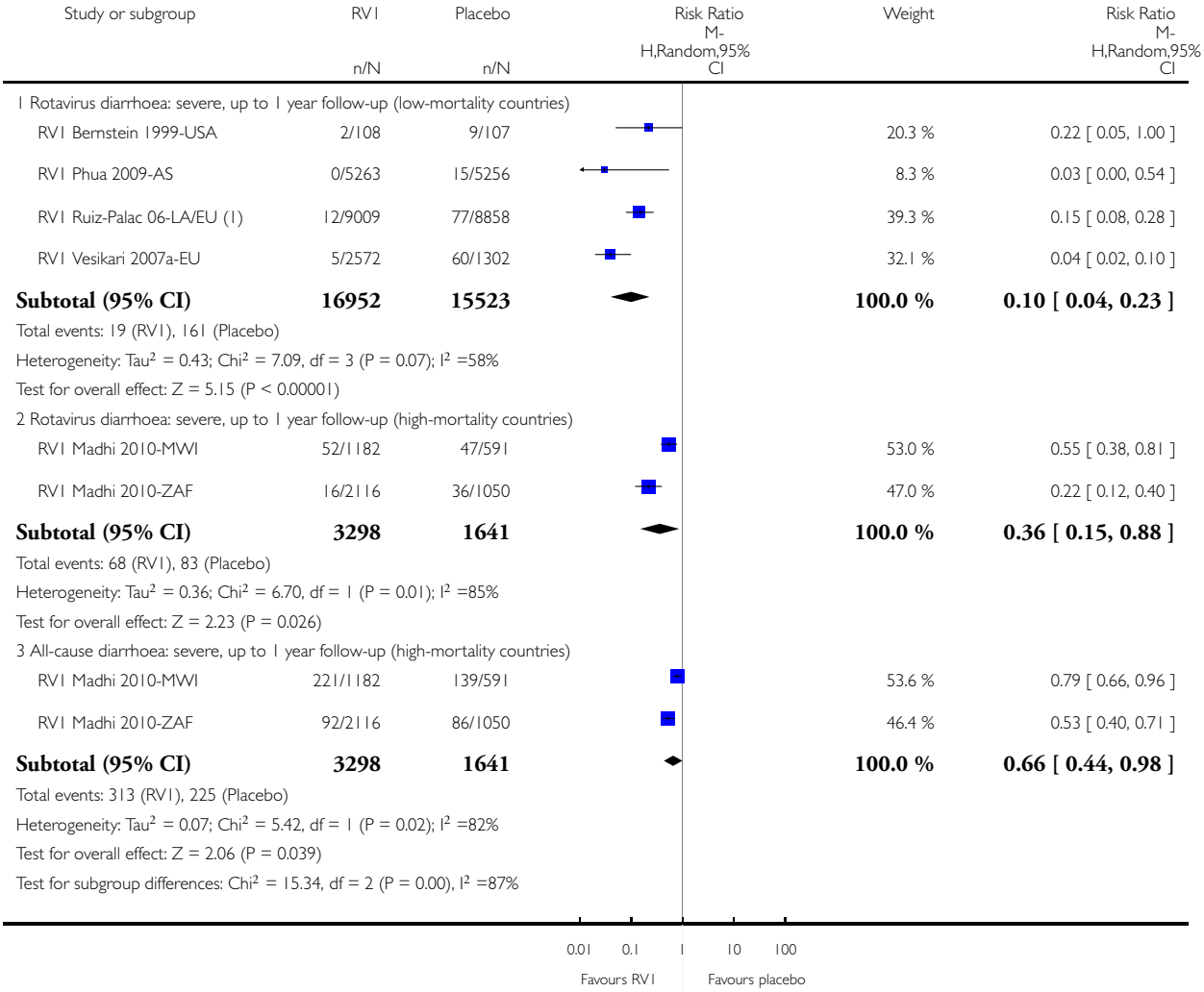
Study or subgroup	RV1 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Severe rotavirus diarrhoea (2 year follow-up) breast fed infants					
RV1 Vesikari 2007a-EU	23/2005	130/1041		100.0 %	0.09 [0.06, 0.14]
Subtotal (95% CI)	**2005**	**1041**		**100.0 %**	**0.09 [0.06, 0.14]**
Total events: 23 (RV1), 130 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 10.71 (P < 0.00001)					
2 Severe rotavirus diarrhoea (2 year follow-up): formula fed infants					
RV1 Vesikari 2007a-EU	1/567	24/261		100.0 %	0.02 [0.00, 0.14]
Subtotal (95% CI)	**567**	**261**		**100.0 %**	**0.02 [0.00, 0.14]**
Total events: 1 (RV1), 24 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.88 (P = 0.00010)					
Test for subgroup differences: Chi^2 = 2.26, df = 1 (P = 0.13), I^2 =56%					

Analysis 1.38. Comparison 1 RV1 versus placebo, Outcome 38 Sensitivity analysis: allocation concealment.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 1 RV1 versus placebo

Outcome: 38 Sensitivity analysis: allocation concealment



(1) This multinational study includes 12 Latin America countries, two of them with high mortality (Nicaragua and Peru)

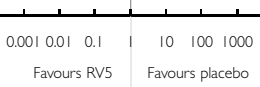
Analysis 2.1. Comparison 2 RV5 versus placebo, Outcome 1 Rotavirus diarrhoea: severe (up to 1 year follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 1 Rotavirus diarrhoea: severe (up to 1 year follow-up)

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-mortality countries (WHO strata A % B)					
RV5 Block 2007-EU/USA	0/551	6/564		5.8 %	0.08 [0.00, 1.39]
RV5 Clark 2004-USA	0/187	8/183		7.7 %	0.06 [0.00, 0.99]
RV5 Zaman 2010-VNM (1)	2/435	7/424		6.4 %	0.28 [0.06, 1.33]
Subtotal (95% CI)	**1173**	**1171**		**19.9 %**	**0.13 [0.04, 0.45]**
Total events: 2 (RV5), 21 (Placebo)					
Heterogeneity: Chi^2 = 1.30, df = 2 (P = 0.52); I^2 =0.0%					
Test for overall effect: Z = 3.26 (P = 0.0011)					
2 High-mortality countries (WHO strata D % E)					
RV5 Armah 2010-GHA (2)	15/981	42/989		37.7 %	0.36 [0.20, 0.64]
RV5 Armah 2010-KEN (3)	2/575	12/573		10.8 %	0.17 [0.04, 0.74]
RV5 Armah 2010-MLI (4)	4/845	4/843		3.6 %	1.00 [0.25, 3.98]
RV5 Zaman 2010-BGD (5)	17/556	31/554		28.0 %	0.55 [0.31, 0.98]
Subtotal (95% CI)	**2957**	**2959**		**80.1 %**	**0.43 [0.29, 0.62]**
Total events: 38 (RV5), 89 (Placebo)					
Heterogeneity: Chi^2 = 4.01, df = 3 (P = 0.26); I^2 =25%					
Test for overall effect: Z = 4.44 (P < 0.00001)					
Total (95% CI)	**4130**	**4130**		**100.0 %**	**0.37 [0.26, 0.53]**
Total events: 40 (RV5), 110 (Placebo)					
Heterogeneity: Chi^2 = 7.72, df = 6 (P = 0.26); I^2 =22%					
Test for overall effect: Z = 5.51 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 3.22, df = 1 (P = 0.07), I^2 =69%					



(1) Data from RV5 Zaman 2010-AS for Vietnam only

(2) Total number of participants taken from Tapia et al. 2012, Table 4, data for Ghana only.

(3) Total number of participants taken from Tapia et al. 2012, Table 4, data for Kenya only.

(4) Total number of participants taken from Tapia et al. 2012, Table 4, data for Mali only.

(5) Data from RV5 Zaman 2010-AS for Bangladesh only

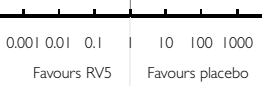
Analysis 2.2. Comparison 2 RV5 versus placebo, Outcome 2 Rotavirus diarrhoea: severe (up to 2 years follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 2 Rotavirus diarrhoea: severe (up to 2 years follow-up)

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low-mortality countries (WHO strata A % B)					
RV5 NCT00718237 2010-JPN	0/381	10/381		2.1 %	0.05 [0.00, 0.81]
RV5 Vesikari 2006b-INT (1)	2/813	17/756		6.6 %	0.11 [0.03, 0.47]
RV5 Zaman 2010-VNM (2)	5/435	15/424		11.1 %	0.32 [0.12, 0.89]
Subtotal (95% CI)	**1629**	**1561**		**19.8 %**	**0.18 [0.07, 0.50]**
Total events: 7 (RV5), 42 (Placebo)					
Heterogeneity: Tau^2 = 0.23; Chi^2 = 2.73, df = 2 (P = 0.26); I^2 =27%					
Test for overall effect: Z = 3.31 (P = 0.00092)					
2 High-mortality countries (WHO strata D % E)					
RV5 Armah 2010-GHA (3)	26/982	57/989		22.0 %	0.46 [0.29, 0.72]
RV5 Armah 2010-KEN (4)	5/569	14/568		11.0 %	0.36 [0.13, 0.98]
RV5 Armah 2010-MLI (5)	48/832	58/835		24.1 %	0.83 [0.57, 1.20]
RV5 Zaman 2010-BGD (6)	33/556	56/554		23.1 %	0.59 [0.39, 0.89]
Subtotal (95% CI)	**2939**	**2946**		**80.2 %**	**0.59 [0.43, 0.82]**
Total events: 112 (RV5), 185 (Placebo)					
Heterogeneity: Tau^2 = 0.05; Chi^2 = 5.28, df = 3 (P = 0.15); I^2 =43%					
Test for overall effect: Z = 3.19 (P = 0.0014)					
Total (95% CI)	**4568**	**4507**		**100.0 %**	**0.46 [0.30, 0.70]**
Total events: 119 (RV5), 227 (Placebo)					
Heterogeneity: Tau^2 = 0.16; Chi^2 = 15.15, df = 6 (P = 0.02); I^2 =60%					
Test for overall effect: Z = 3.63 (P = 0.00028)					
Test for subgroup differences: Chi^2 = 4.79, df = 1 (P = 0.03), I^2 =79%					



(1) This study was conducted mainly in European and Latin American low mortality countries, but also in high mortality Guatemala

(2) Data from RV5 Zaman 2010-AS for Vietnam only

(3) Total number of participants taken from Tapia et al. 2012, Table 4, data for Ghana only.

(4) Total number of participants taken from Tapia et al. 2012, Table 4, data for Kenya only.

(5) Total number of participants taken from Tapia et al. 2012, Table 4, data for Mali only.

(6) Data from RV5 Zaman 2010-AS for Bangladesh only

Analysis 2.3. Comparison 2 RV5 versus placebo, Outcome 3 All-cause diarrhoea: severe cases (up to 1 year follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 3 All-cause diarrhoea: severe cases (up to 1 year follow-up)

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low-mortality countries (WHO stratum A)					
RV5 Vesikari 2006a-FIN	23/767	28/262		23.3 %	0.28 [0.16, 0.48]
Subtotal (95% CI)	**767**	**262**		**23.3 %**	**0.28 [0.16, 0.48]**
Total events: 23 (RV5), 28 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.67 (P < 0.00001)					
2 High-mortality countries (WHO strata D % E)					
RV5 Armah 2010-GHA (1)	49/753	78/737		27.5 %	0.61 [0.44, 0.87]
RV5 Armah 2010-KEN (2)	21/481	22/477		22.1 %	0.95 [0.53, 1.70]
RV5 Armah 2010-MLI (3)	55/823	56/814		27.1 %	0.97 [0.68, 1.39]
Subtotal (95% CI)	**2057**	**2028**		**76.7 %**	**0.80 [0.58, 1.11]**
Total events: 125 (RV5), 156 (Placebo)					
Heterogeneity: Tau^2 = 0.04; Chi^2 = 3.70, df = 2 (P = 0.16); I^2 =46%					
Test for overall effect: Z = 1.32 (P = 0.19)					
Total (95% CI)	**2824**	**2290**		**100.0 %**	**0.64 [0.39, 1.06]**
Total events: 148 (RV5), 184 (Placebo)					
Heterogeneity: Tau^2 = 0.21; Chi^2 = 15.94, df = 3 (P = 0.001); I^2 =81%					
Test for overall effect: Z = 1.74 (P = 0.081)					
Test for subgroup differences: Chi^2 = 10.95, df = 1 (P = 0.00), I^2 =91%					

(1) Data collected from Tapia et al. 2012, Table 3, data for Ghana only.

(2) Data collected from Tapia et al. 2012, Table 3, data for Kenya only.

(3) Data collected from Tapia et al. 2012, Table 3, data for Mali only.

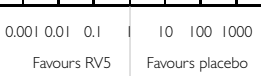
Analysis 2.4. Comparison 2 RV5 versus placebo, Outcome 4 All-cause diarrhoea: severe cases (up to 2 years follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 4 All-cause diarrhoea: severe cases (up to 2 years follow-up)

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-mortality countries (WHO strata A % B)					
RV5 Vesikari 2006a-FIN	0/767	4/262		1.7 %	0.04 [0.00, 0.70]
Subtotal (95% CI)	**767**	**262**		**1.7 %**	**0.04 [0.00, 0.70]**
Total events: 0 (RV5), 4 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.20 (P = 0.028)					
2 High-mortality countries (WHO strata D % E)					
RV5 Armah 2010-GHA (1)	80/747	101/725		26.0 %	0.77 [0.58, 1.01]
RV5 Armah 2010-KEN (2)	25/472	29/472		7.4 %	0.86 [0.51, 1.45]
RV5 Armah 2010-MLI (3)	147/797	148/795		37.6 %	0.99 [0.81, 1.22]
RV5 Zaman 2010-AS (4)	81/991	107/978		27.3 %	0.75 [0.57, 0.98]
Subtotal (95% CI)	**3007**	**2970**		**98.3 %**	**0.85 [0.75, 0.98]**
Total events: 333 (RV5), 385 (Placebo)					
Heterogeneity: Chi^2 = 3.47, df = 3 (P = 0.32); I^2 =14%					
Test for overall effect: Z = 2.26 (P = 0.024)					
Total (95% CI)	**3774**	**3232**		**100.0 %**	**0.84 [0.73, 0.96]**
Total events: 333 (RV5), 389 (Placebo)					
Heterogeneity: Chi^2 = 7.89, df = 4 (P = 0.10); I^2 =49%					
Test for overall effect: Z = 2.51 (P = 0.012)					
Test for subgroup differences: Chi^2 = 4.36, df = 1 (P = 0.04), I^2 =77%					



(1) Data collected from Tapia et al. 2012, Table 3, data for Ghana only.

(2) Data collected from Tapia et al. 2012, Table 3, data for Kenya only.

(3) Data collected from Tapia et al. 2012, Table 3, data for Mali only.

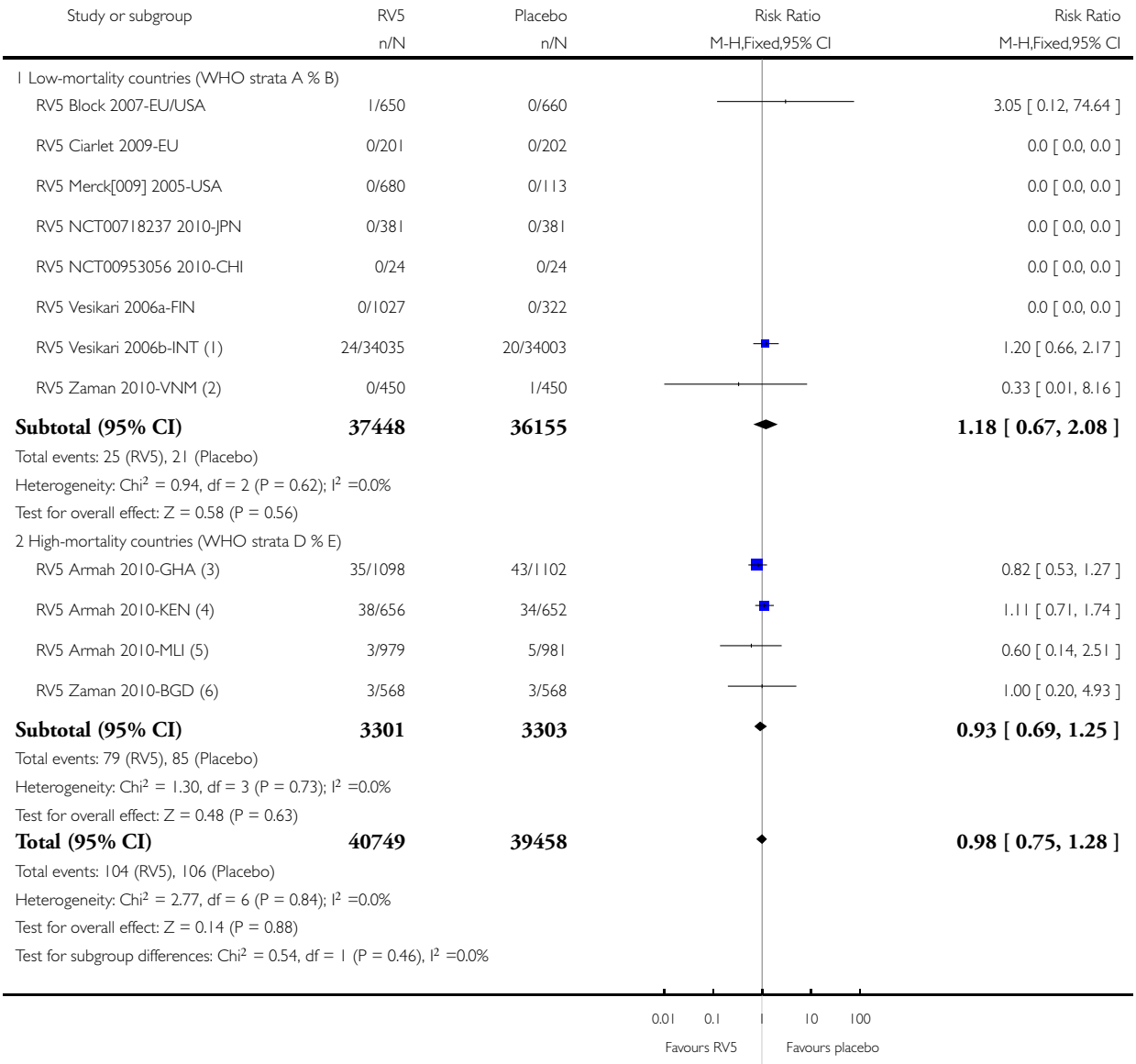
(4) This study was mainly conducted in high mortality Bangladesh, but also in low mortality Vietnam.

Analysis 2.5. Comparison 2 RV5 versus placebo, Outcome 5 All-cause death.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 5 All-cause death



(1) This study was conducted mainly in European and Latin American low mortality countries, but also in high mortality Guatemala

(2) Data from RV5 Zaman 2010-AS for Vietnam only

(3) Data from RV5 Armah 2010-AF for Ghana only

(4) Data from RV5 Armah 2010-AF for Kenya only

(5) Data from RV5 Armah 2010-AF for Mali only

(6) Data from RV5 Zaman 2010-AS for Bangladesh only

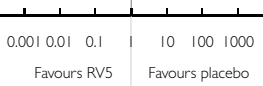
Analysis 2.6. Comparison 2 RV5 versus placebo, Outcome 6 All serious adverse events.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 6 All serious adverse events

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-mortality countries (WHO strata A % B)					
RV5 Block 2007-EU/USA	21/650	27/660		2.7 %	0.79 [0.45, 1.38]
RV5 Ciarlet 2009-EU	3/201	6/202		0.6 %	0.50 [0.13, 1.98]
RV5 Kim 2008-KOR	6/115	7/63		0.9 %	0.47 [0.16, 1.34]
RV5 NCT00718237 2010-JPN	7/380	9/381		0.9 %	0.78 [0.29, 2.07]
RV5 NCT00953056 2010-CHI	0/24	4/24		0.5 %	0.11 [0.01, 1.96]
RV5 Vesikari 2006b-INT (1)	803/34035	859/34003		87.7 %	0.93 [0.85, 1.03]
RV5 Zaman 2010-VNM (2)	9/450	3/450		0.3 %	3.00 [0.82, 11.01]
Subtotal (95% CI)	**35855**	**35783**		**93.7 %**	**0.92 [0.84, 1.01]**
Total events: 849 (RV5), 915 (Placebo)					
Heterogeneity: Chi^2 = 8.08, df = 6 (P = 0.23); I^2 =26%					
Test for overall effect: Z = 1.69 (P = 0.091)					
2 High-mortality countries (WHO strata D % E)					
RV5 Armah 2010-GHA (3)	17/1098	18/1102		1.8 %	0.95 [0.49, 1.83]
RV5 Armah 2010-KEN (4)	20/649	21/643		2.2 %	0.94 [0.52, 1.72]
RV5 Armah 2010-MLI (5)	5/979	6/981		0.6 %	0.84 [0.26, 2.73]
RV5 Zaman 2010-BGD (6)	16/568	17/568		1.7 %	0.94 [0.48, 1.84]



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Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**3294**	**3294**		**6.3 %**	**0.93 [0.66, 1.33]**
Total events: 58 (RV5), 62 (Placebo)					
Heterogeneity: Chi^2 = 0.04, df = 3 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 0.38 (P = 0.70)					
Total (95% CI)	**39149**	**39077**		**100.0 %**	**0.92 [0.85, 1.01]**
Total events: 907 (RV5), 977 (Placebo)					
Heterogeneity: Chi^2 = 8.12, df = 10 (P = 0.62); I^2 =0.0%					
Test for overall effect: Z = 1.73 (P = 0.083)					
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.95), I^2 =0.0%					

(1) This study was conducted mainly in European and Latin American low mortality countries, but also in high mortality Guatemala

(2) Data from RV5 Zaman 2010-AS for Vietnam only

(3) Data from RV5 Armah 2010-AF for Ghana only

(4) Data from RV5 Armah 2010-AF for Kenya only

(5) Data from RV5 Armah 2010-AF for Mali only

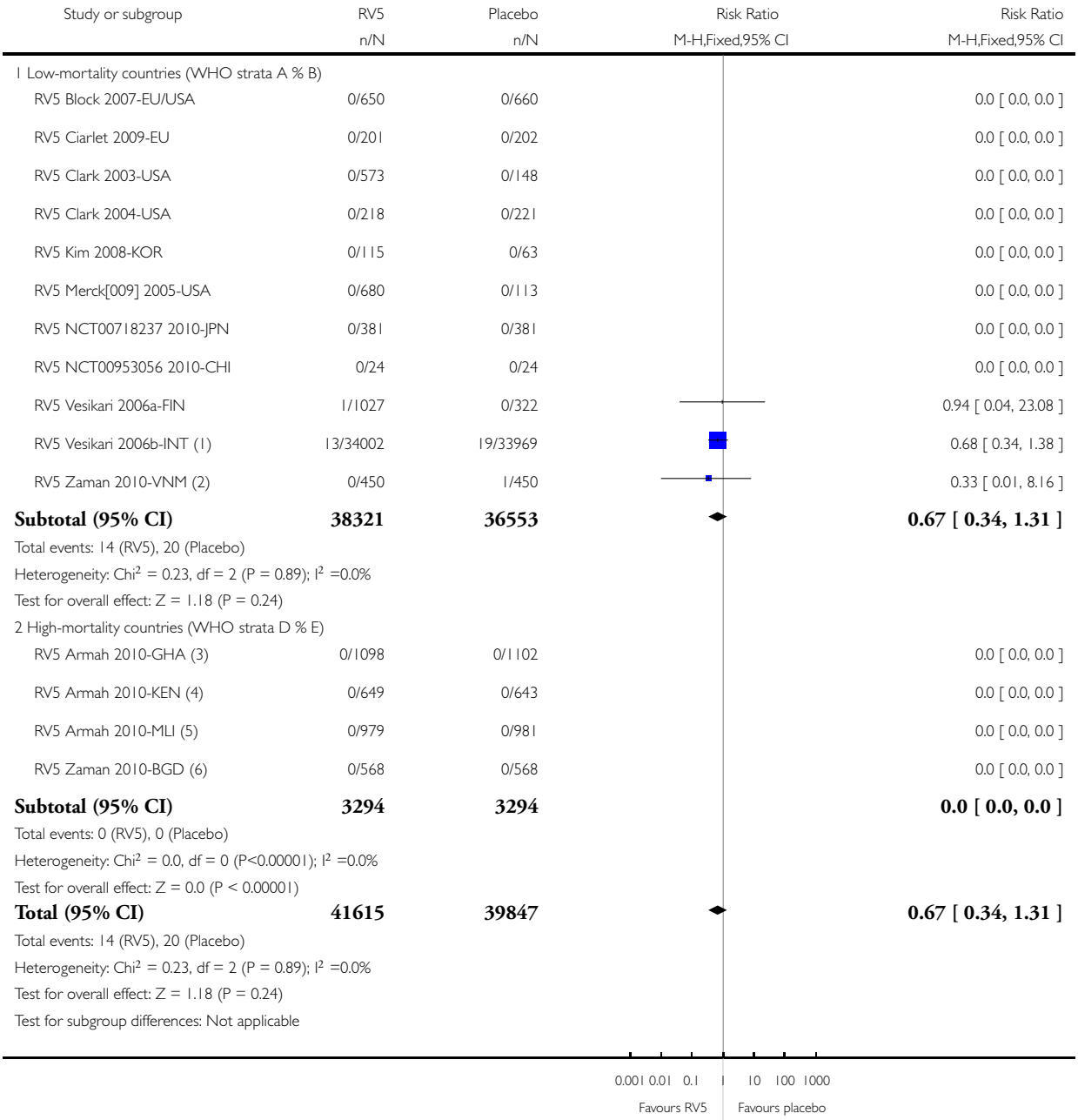
(6) Data from RV5 Zaman 2010-AS for Bangladesh only

Analysis 2.7. Comparison 2 RV5 versus placebo, Outcome 7 Serious adverse events: intussusception.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 7 Serious adverse events: intussusception



(1) This study was conducted mainly in European and Latin American low mortality countries, but also in high mortality Guatemala

(2) Data from RV5 Zaman 2010-AS for Vietnam only

(3) Data from RV5 Armah 2010-AF for Ghana only

(4) Data from RV5 Armah 2010-AF for Kenya only

(5) Data from RV5 Armah 2010-AF for Mali only

(6) Data from RV5 Zaman 2010-AS for Bangladesh only

Analysis 2.8. Comparison 2 RV5 versus placebo, Outcome 8 Rotavirus diarrhoea: of any severity (up to 1 year follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 8 Rotavirus diarrhoea: of any severity (up to 1 year follow-up)

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low-mortality countries (WHO strata A % B)					
RV5 Block 2007-EU/USA	21/551	63/564		16.5 %	0.34 [0.21, 0.55]
RV5 Clark 2003-USA	5/342	7/114		6.9 %	0.24 [0.08, 0.74]
RV5 Clark 2004-USA	11/187	39/183		13.4 %	0.28 [0.15, 0.52]
RV5 Vesikari 2006b-INT (1)	82/2834	315/2839		21.4 %	0.26 [0.21, 0.33]
Subtotal (95% CI)	**3914**	**3700**		**58.2 %**	**0.27 [0.22, 0.33]**
Total events: 119 (RV5), 424 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.03, df = 3 (P = 0.79); I^2 =0.0%					
Test for overall effect: Z = 12.78 (P < 0.00001)					
2 High-mortality countries (WHO strata D % E)					
RV5 Armah 2010-GHA (2)	31/981	70/989		17.9 %	0.45 [0.30, 0.68]
RV5 Armah 2010-KEN (3)	6/575	21/573		9.3 %	0.28 [0.12, 0.70]
RV5 Armah 2010-MLI (4)	22/845	24/843		14.6 %	0.91 [0.52, 1.62]
Subtotal (95% CI)	**2401**	**2405**		**41.8 %**	**0.52 [0.28, 0.94]**
Total events: 59 (RV5), 115 (Placebo)					
Heterogeneity: Tau^2 = 0.18; Chi^2 = 6.02, df = 2 (P = 0.05); I^2 =67%					
Test for overall effect: Z = 2.16 (P = 0.031)					

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Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total (95% CI)	**6315**	**6105**	◆	**100.0 %**	**0.36 [0.26, 0.52]**
Total events: 178 (RV5), 539 (Placebo)					
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 18.87$, df = 6 (P = 0.004); $I^2 = 68\%$					
Test for overall effect: Z = 5.62 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 3.85$, df = 1 (P = 0.05), $I^2 = 74\%$					

(1) This study was conducted mainly in European and Latin American low mortality countries, but also in high mortality Guatemala

(2) Data collected from Tapia et al. 2012, Table 4 for Ghana only.

(3) Data collected from Tapia et al. 2012, Table 4 for Kenya only.

(4) Data collected from Tapia et al. 2012, Table 4 for Mali only.

Analysis 2.9. Comparison 2 RV5 versus placebo, Outcome 9 Rotavirus diarrhoea: of any severity (up to 2 years follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 9 Rotavirus diarrhoea: of any severity (up to 2 years follow-up)

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low-mortality countries (WHO strata A % B)					
RV5 NCT00718237 2010-JPN	7/355	27/356		9.6 %	0.26 [0.11, 0.59]
RV5 Vesikari 2006b-INT (1)	36/813	88/756		18.3 %	0.38 [0.26, 0.55]
Subtotal (95% CI)	**1168**	**1112**		**28.0 %**	**0.36 [0.25, 0.50]**
Total events: 43 (RV5), 115 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.69$, df = 1 (P = 0.41); $I^2 = 0.0\%$					
Test for overall effect: Z = 5.94 (P < 0.00001)					
2 High-mortality countries (WHO strata D % E)					
RV5 Armah 2010-GHA (2)	46/982	88/989		19.0 %	0.53 [0.37, 0.74]
RV5 Armah 2010-KEN (3)	9/569	24/568		10.5 %	0.37 [0.18, 0.80]
RV5 Armah 2010-MLI (4)	151/832	182/835		22.3 %	0.83 [0.69, 1.01]
RV5 Zaman 2010-AS (5)	65/991	109/978		20.2 %	0.59 [0.44, 0.79]
Subtotal (95% CI)	**3374**	**3370**		**72.0 %**	**0.61 [0.45, 0.83]**
Total events: 271 (RV5), 403 (Placebo)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 9.72$, df = 3 (P = 0.02); $I^2 = 69\%$					
Test for overall effect: Z = 3.21 (P = 0.0013)					
Total (95% CI)	**4542**	**4482**		**100.0 %**	**0.51 [0.36, 0.70]**
Total events: 314 (RV5), 518 (Placebo)					
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 22.80$, df = 5 (P = 0.00037); $I^2 = 78\%$					
Test for overall effect: Z = 4.07 (P = 0.000047)					
Test for subgroup differences: $Chi^2 = 5.43$, df = 1 (P = 0.02), $I^2 = 82\%$					

(1) This study was conducted mainly in European and Latin American low mortality countries, but also in high mortality Guatemala

(2) Data collected from Tapia et al. 2012, Table 4 for Ghana only.

(3) Data collected from Tapia et al. 2012, Table 4 for Kenya only.

(4) Data collected from Tapia et al. 2012, Table 4 for Mali only.

(5) This study was mainly conducted in high mortality Bangladesh, but also in low mortality Vietnam.

Analysis 2.10. Comparison 2 RV5 versus placebo, Outcome 10 All-cause diarrhoea: of any severity (up to 1 year follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 10 All-cause diarrhoea: of any severity (up to 1 year follow-up)

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-mortality countries (WHO strata A % B)					
RV5 Vesikari 2006a-FIN	51/766	43/264		44.0 %	0.41 [0.28, 0.60]
Subtotal (95% CI)	**766**	**264**		**44.0 %**	**0.41 [0.28, 0.60]**
Total events: 51 (RV5), 43 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.60 (P < 0.00001)					
2 High-mortality countries (WHO stratum E)					
RV5 Armah 2010-KEN (1)	66/525	82/534		56.0 %	0.82 [0.61, 1.11]
Subtotal (95% CI)	**525**	**534**		**56.0 %**	**0.82 [0.61, 1.11]**
Total events: 66 (RV5), 82 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.30 (P = 0.19)					
Total (95% CI)	**1291**	**798**		**100.0 %**	**0.64 [0.51, 0.81]**
Total events: 117 (RV5), 125 (Placebo)					
Heterogeneity: Chi^2 = 7.89, df = 1 (P = 0.005); I^2 =87%					
Test for overall effect: Z = 3.77 (P = 0.00016)					
Test for subgroup differences: Chi^2 = 7.86, df = 1 (P = 0.01), I^2 =87%					

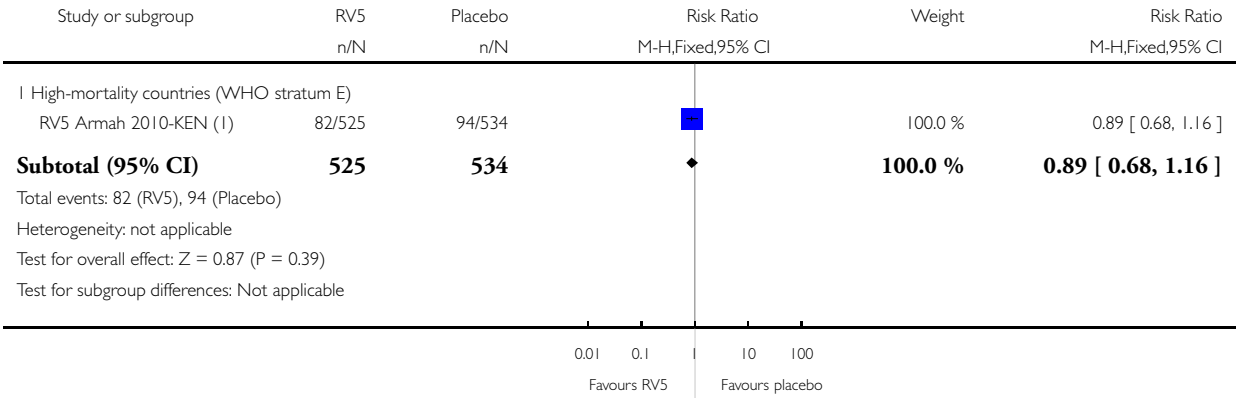
(1) Data from RV5 Armah 2010-AF for Kenya only

Analysis 2.11. Comparison 2 RV5 versus placebo, Outcome 11 All-cause diarrhoea: of any severity (up to 2 years follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 11 All-cause diarrhoea: of any severity (up to 2 years follow-up)



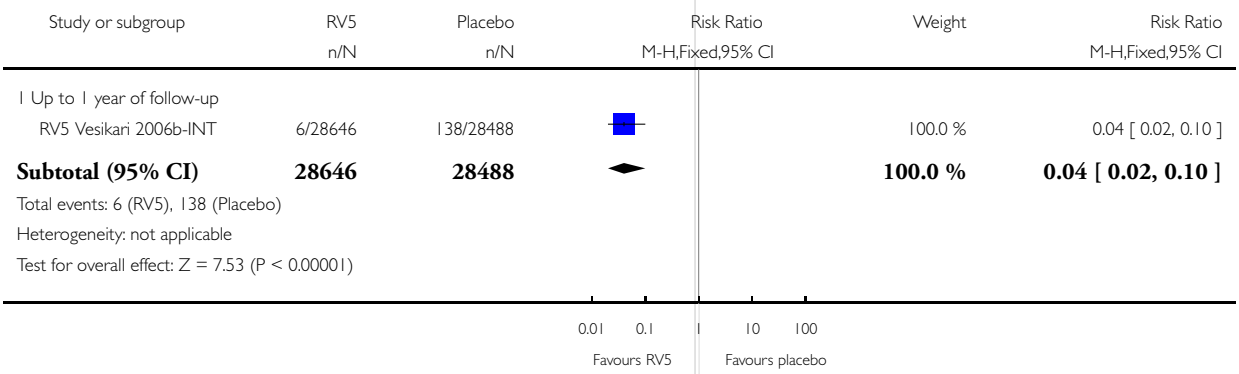
(1) Data from RV5 Armah 2010-AF for Kenya only

Analysis 2.12. Comparison 2 RV5 versus placebo, Outcome 12 Rotavirus diarrhoea: requiring hospitalization.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 12 Rotavirus diarrhoea: requiring hospitalization



Analysis 2.13. Comparison 2 RV5 versus placebo, Outcome 13 Rotavirus diarrhoea: requiring medical attention.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 13 Rotavirus diarrhoea: requiring medical attention

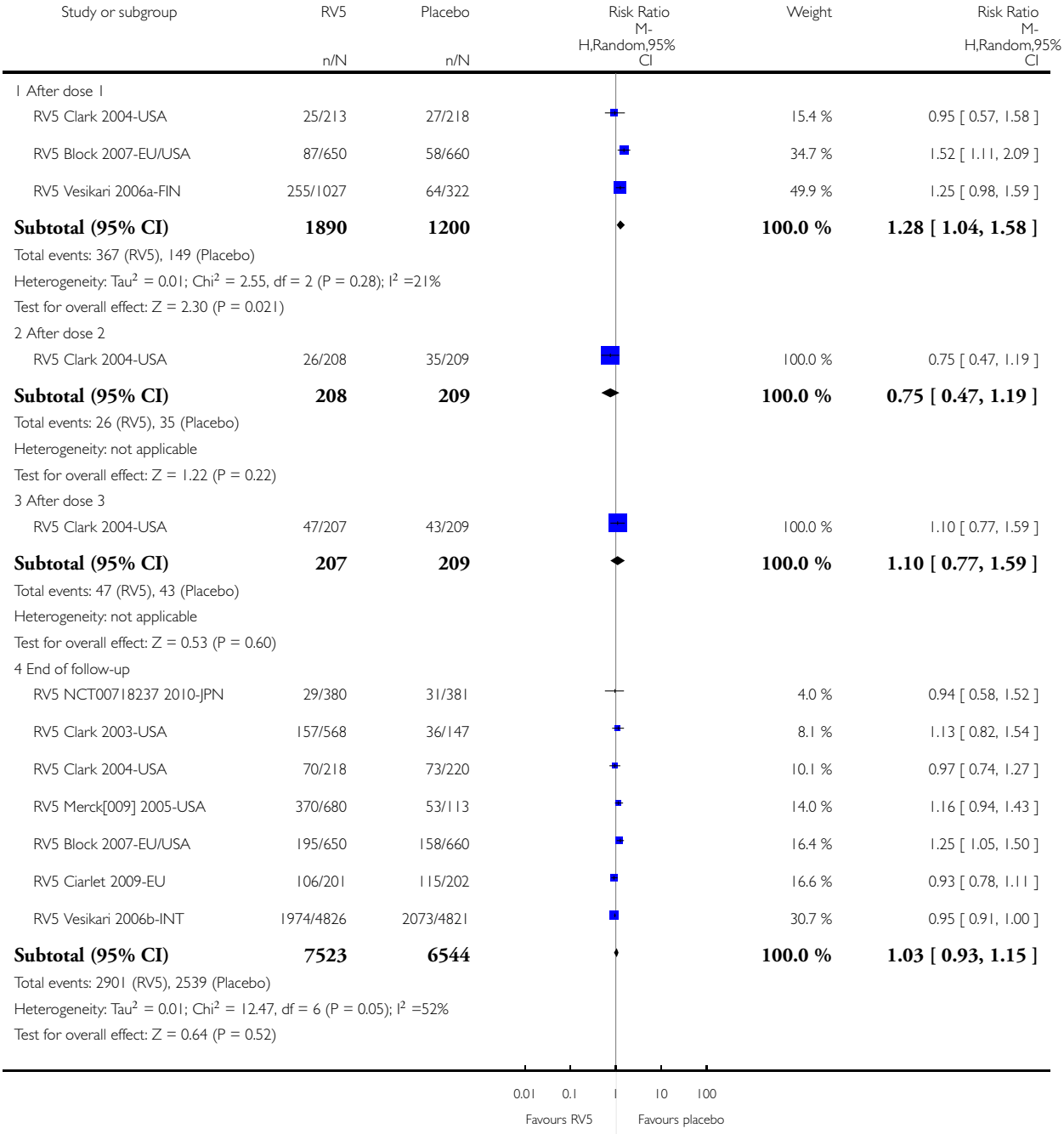
Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Up to 1 year of follow-up					
RV5 Vesikari 2006b-INT	13/28646	191/28488		100.0 %	0.07 [0.04, 0.12]
Subtotal (95% CI)	**28646**	**28488**		**100.0 %**	**0.07 [0.04, 0.12]**
Total events: 13 (RV5), 191 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 9.40 (P < 0.00001)					

Analysis 2.14. Comparison 2 RV5 versus placebo, Outcome 14 Reactogenicity: fever.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 14 Reactogenicity: fever

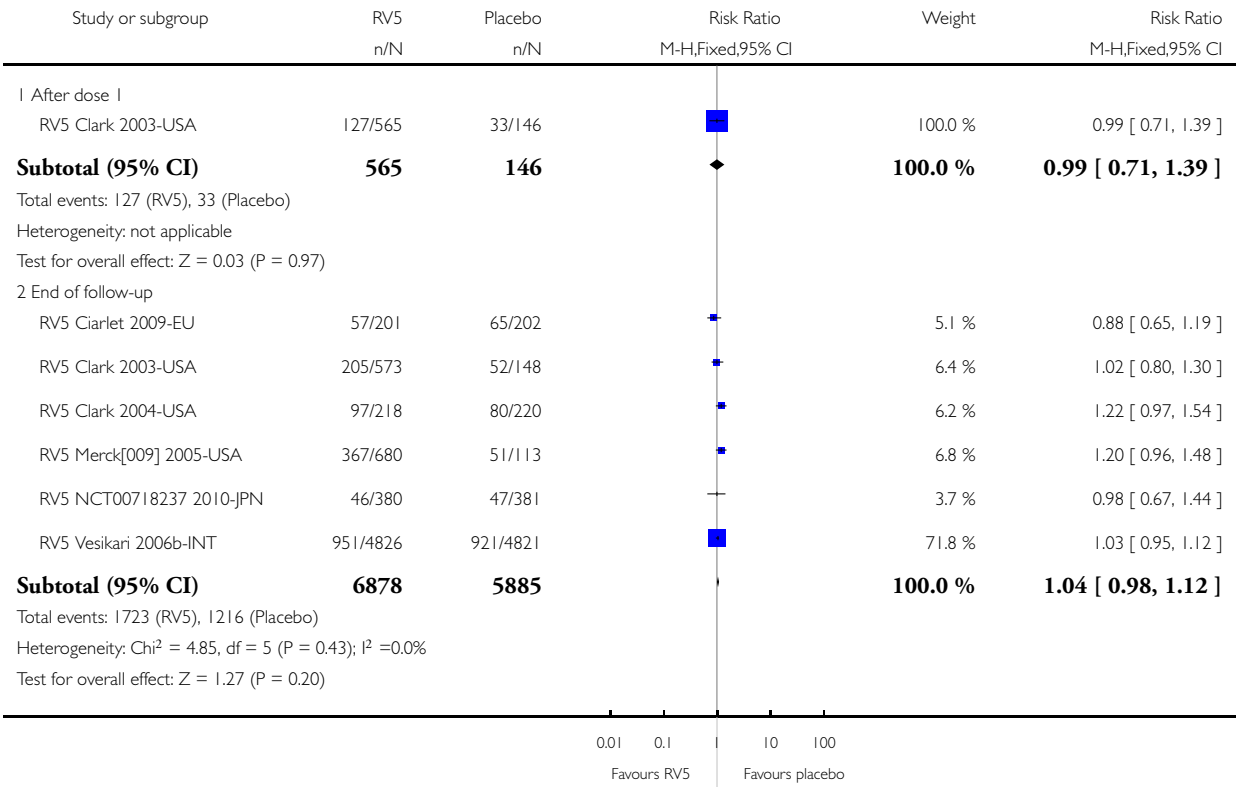


Analysis 2.15. Comparison 2 RV5 versus placebo, Outcome 15 Reactogenicity: diarrhoea.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 15 Reactogenicity: diarrhoea



Analysis 2.16. Comparison 2 RV5 versus placebo, Outcome 16 Reactogenicity: vomiting.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 16 Reactogenicity: vomiting

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 After dose 1					
RV5 Clark 2003-USA	91/565	27/146		100.0 %	0.87 [0.59, 1.29]
Subtotal (95% CI)	**565**	**146**		**100.0 %**	**0.87 [0.59, 1.29]**
Total events: 91 (RV5), 27 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.70 (P = 0.49)					
2 End of follow-up					
RV5 Ciarlet 2009-EU	62/201	49/202		5.8 %	1.27 [0.92, 1.75]
RV5 Clark 2003-USA	171/573	41/148		7.7 %	1.08 [0.81, 1.44]
RV5 Clark 2004-USA	58/218	52/220		6.2 %	1.13 [0.81, 1.56]
RV5 NCT00718237 2010-JPN	31/380	29/381		3.4 %	1.07 [0.66, 1.74]
RV5 Vesikari 2006b-INT	618/4826	646/4821		76.8 %	0.96 [0.86, 1.06]
Subtotal (95% CI)	**6198**	**5772**		**100.0 %**	**1.00 [0.91, 1.09]**
Total events: 940 (RV5), 817 (Placebo)					
Heterogeneity: Chi^2 = 3.77, df = 4 (P = 0.44); I^2 =0.0%					
Test for overall effect: Z = 0.05 (P = 0.96)					

Analysis 2.17. Comparison 2 RV5 versus placebo, Outcome 17 Adverse events requiring discontinuation (end of follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 17 Adverse events requiring discontinuation (end of follow-up)

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
RV5 Armah 2010-AF	9/2733	15/2735		0.60 [0.26, 1.37]
RV5 Block 2007-EU/USA	1/650	5/660		0.20 [0.02, 1.73]
RV5 Ciarlet 2009-EU	1/201	0/202		3.01 [0.12, 73.57]
RV5 Clark 2004-USA	4/218	1/221		4.06 [0.46, 35.99]
RV5 Kim 2008-KOR	0/115	0/63		0.0 [0.0, 0.0]
RV5 Merck[009] 2005-USA	1/680	1/113		0.17 [0.01, 2.64]
RV5 NCT00718237 2010-JPN	1/381	3/381		0.33 [0.03, 3.19]
RV5 NCT00953056 2010-CHI	0/24	1/24		0.33 [0.01, 7.80]
RV5 Zaman 2010-AS	1/1018	0/1018		3.00 [0.12, 73.56]
Total (95% CI)	**6020**	**5417**		**0.67 [0.38, 1.19]**
Total events: 18 (RV5), 26 (Placebo)				
Heterogeneity: Chi^2 = 7.10, df = 7 (P = 0.42); I^2 =1%				
Test for overall effect: Z = 1.37 (P = 0.17)				
Test for subgroup differences: Not applicable				

Analysis 2.18. Comparison 2 RV5 versus placebo, Outcome 18 Immunogenicity: rotavirus vaccine shedding (after dose 3).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 18 Immunogenicity: rotavirus vaccine shedding (after dose 3)

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
RV5 Clark 2003-USA	277/355	13/93		5.58 [3.36, 9.27]
RV5 Clark 2004-USA	104/159	2/155		50.69 [12.73, 201.81]
RV5 NCT00953056 2010-CHI	6/23	0/24		13.54 [0.81, 227.50]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**

Total events: 387 (RV5), 15 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 ($P<0.00001$); $I^2 = 0.0\%$

Test for overall effect: $Z = 0.0$ ($P < 0.00001$)

Test for subgroup differences: Not applicable

Analysis 2.19. Comparison 2 RV5 versus placebo, Outcome 19 Immunogenicity: seroconversion (after dose 3).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 19 Immunogenicity: seroconversion (after dose 3)

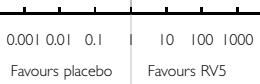
Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
RV5 Armah 2010-AF	148/189	34/169		3.89 [2.86, 5.31]
RV5 Block 2007-EU/USA	64/67	9/73		7.75 [4.19, 14.32]
RV5 Ciarlet 2009-EU	184/201	12/202		15.41 [8.89, 26.72]
RV5 Clark 2003-USA	404/455	3/113		33.44 [10.95, 102.19]
RV5 Clark 2004-USA	162/185	3/185		54.00 [17.55, 166.11]
RV5 Vesikari 2006a-FIN	959/1027	43/322		6.99 [5.29, 9.24]
RV5 Vesikari 2006b-INT	180/189	23/161		6.67 [4.56, 9.75]
RV5 Zaman 2010-AS	115/131	24/132		4.83 [3.34, 6.97]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**

Total events: 2216 (RV5), 151 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 ($P<0.00001$); $I^2 = 0.0\%$

Test for overall effect: $Z = 0.0$ ($P < 0.00001$)

Test for subgroup differences: Not applicable



Analysis 2.20. Comparison 2 RV5 versus placebo, Outcome 20 Drop outs before the end of the trial.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 20 Drop outs before the end of the trial

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
RV5 Armah 2010-AF	376/2733	387/2735		22.9 %	0.97 [0.85, 1.11]
RV5 Block 2007-EU/USA	99/651	96/661		10.2 %	1.05 [0.81, 1.36]
RV5 Clark 2003-USA	97/581	36/150		6.7 %	0.70 [0.50, 0.98]
RV5 Clark 2004-USA	11/218	12/221		1.4 %	0.93 [0.42, 2.06]
RV5 Merck[009] 2005-USA	71/680	16/113		3.3 %	0.74 [0.45, 1.22]
RV5 NCT00718237 2010-JPN	13/381	15/381		1.6 %	0.87 [0.42, 1.80]
RV5 NCT00953056 2010-CHI	2/24	4/24		0.4 %	0.50 [0.10, 2.48]
RV5 Vesikari 2006a-FIN	390/1624	60/322		11.1 %	1.29 [1.01, 1.65]
RV5 Vesikari 2006b-INT	5846/34035	5882/34003		38.9 %	0.99 [0.96, 1.03]
RV5 Zaman 2010-AS	27/1018	40/1018		3.6 %	0.68 [0.42, 1.09]
Total (95% CI)	**41945**	**39628**		**100.0 %**	**0.97 [0.88, 1.07]**

Total events: 6932 (RV5), 6548 (Placebo)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 13.56$, df = 9 (P = 0.14); $I^2 = 34\%$

Test for overall effect: Z = 0.63 (P = 0.53)

Test for subgroup differences: Not applicable

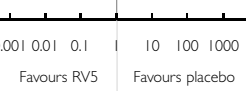
Analysis 2.21. Comparison 2 RV5 versus placebo, Outcome 21 Subgroup analysis: rotavirus diarrhoea of any severity (by G type).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 21 Subgroup analysis: rotavirus diarrhoea of any severity (by G type)

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 G1					
RV5 Block 2007-EU/USA	13/551	53/564		13.8 %	0.25 [0.14, 0.46]
RV5 Clark 2004-USA	10/187	26/183		10.0 %	0.38 [0.19, 0.76]
RV5 Vesikari 2006b-INT	72/2834	286/2839		76.2 %	0.25 [0.20, 0.32]
Subtotal (95% CI)	**3572**	**3586**		**100.0 %**	**0.26 [0.21, 0.33]**
Total events: 95 (RV5), 365 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.14$, df = 2 (P = 0.57); $I^2 = 0.0\%$					
Test for overall effect: Z = 11.87 (P < 0.00001)					
2 G2					
RV5 Clark 2004-USA	1/187	2/183		13.1 %	0.49 [0.04, 5.35]
RV5 Vesikari 2006b-INT	6/2834	17/2839		86.9 %	0.35 [0.14, 0.90]
Subtotal (95% CI)	**3021**	**3022**		**100.0 %**	**0.37 [0.16, 0.88]**
Total events: 7 (RV5), 19 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.06$, df = 1 (P = 0.80); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.26 (P = 0.024)					
3 G3					
RV5 Block 2007-EU/USA	2/551	1/564		33.8 %	2.05 [0.19, 22.51]
RV5 Clark 2004-USA	0/187	10/183		29.0 %	0.05 [0.00, 0.79]
RV5 Vesikari 2006b-INT	1/2834	6/2839		37.3 %	0.17 [0.02, 1.39]
Subtotal (95% CI)	**3572**	**3586**		**100.0 %**	**0.27 [0.03, 2.29]**
Total events: 3 (RV5), 17 (Placebo)					
Heterogeneity: $Tau^2 = 2.04$; $Chi^2 = 4.66$, df = 2 (P = 0.10); $I^2 = 57\%$					
Test for overall effect: Z = 1.20 (P = 0.23)					
4 G4					
RV5 Clark 2004-USA	0/187	1/183		15.8 %	0.33 [0.01, 7.96]
RV5 Vesikari 2006b-INT	3/2834	6/2839		84.2 %	0.50 [0.13, 2.00]
Subtotal (95% CI)	**3021**	**3022**		**100.0 %**	**0.47 [0.13, 1.67]**
Total events: 3 (RV5), 7 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.06$, df = 1 (P = 0.81); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.17 (P = 0.24)					



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Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
5 G9					
RV5 Vesikari 2006b-INT	1/2834	3/2839		100.0 %	0.33 [0.03, 3.21]
Subtotal (95% CI)	**2834**	**2839**		**100.0 %**	**0.33 [0.03, 3.21]**
Total events: 1 (RV5), 3 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.95 (P = 0.34)					
Test for subgroup differences: Chi^2 = 1.31, df = 4 (P = 0.86), I^2 =0.0%					

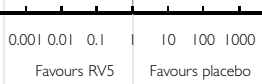
Analysis 2.22. Comparison 2 RV5 versus placebo, Outcome 22 Subgroup analysis: severe cases of rotavirus diarrhoea (by G type).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 22 Subgroup analysis: severe cases of rotavirus diarrhoea (by G type)

Study or subgroup	Favours RV5 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 G1				
RV5 Armah 2010-AF	42/2357	62/2348		0.67 [0.46, 0.99]
RV5 Vesikari 2006b-INT	16/34035	328/34003		0.05 [0.03, 0.08]
Subtotal (95% CI)	**36392**	**36351**		**0.18 [0.01, 2.97]**
Total events: 58 (Favours RV5), 390 (Placebo)				
Heterogeneity: Tau^2 = 4.01; Chi^2 = 77.62, df = 1 (P<0.00001); I^2 =99%				
Test for overall effect: Z = 1.20 (P = 0.23)				
2 G2				
RV5 Armah 2010-AF	32/2357	44/2348		0.72 [0.46, 1.14]
RV5 Vesikari 2006b-INT	1/34035	8/34003		0.12 [0.02, 1.00]
Subtotal (95% CI)	**36392**	**36351**		**0.41 [0.08, 2.09]**



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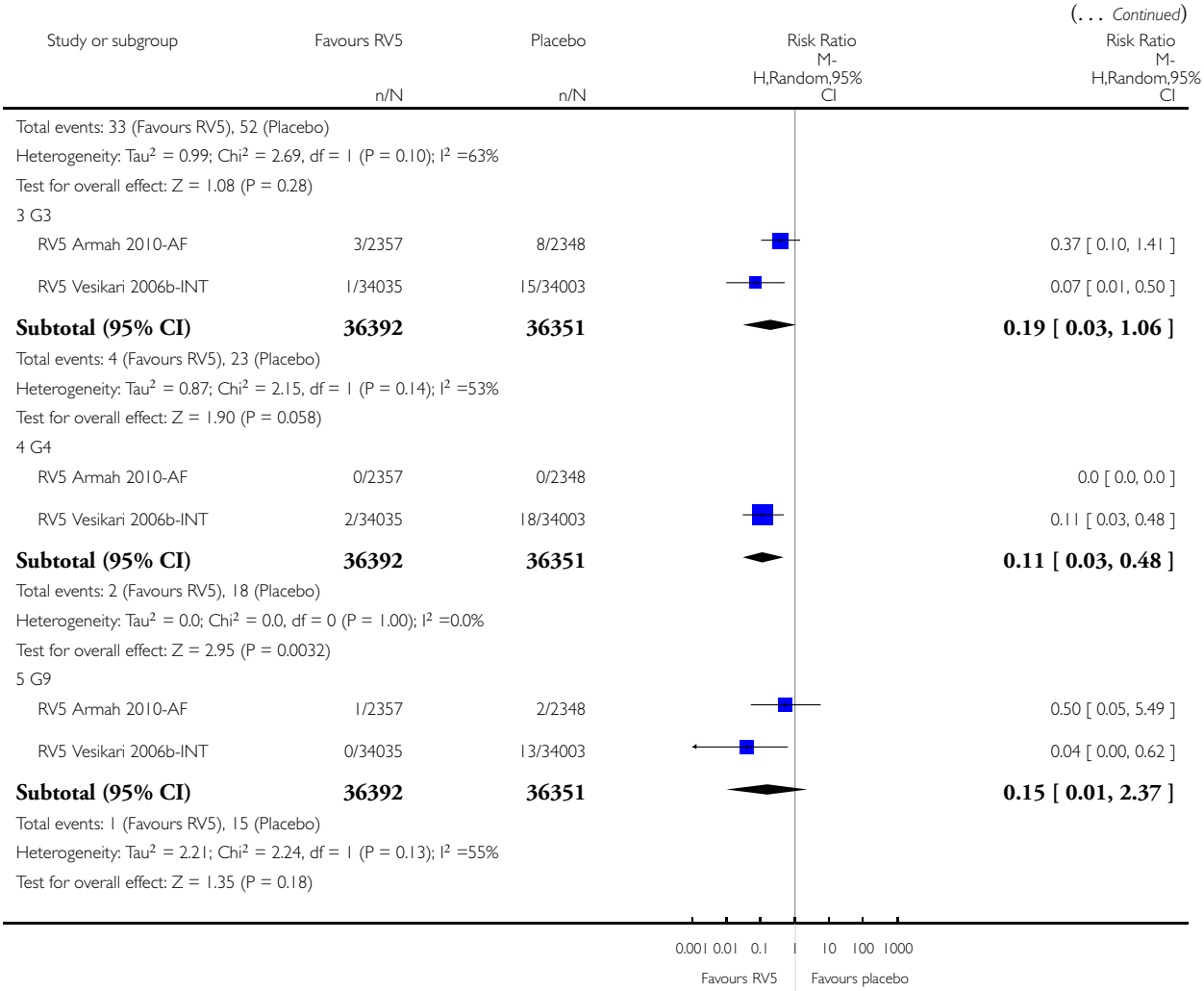
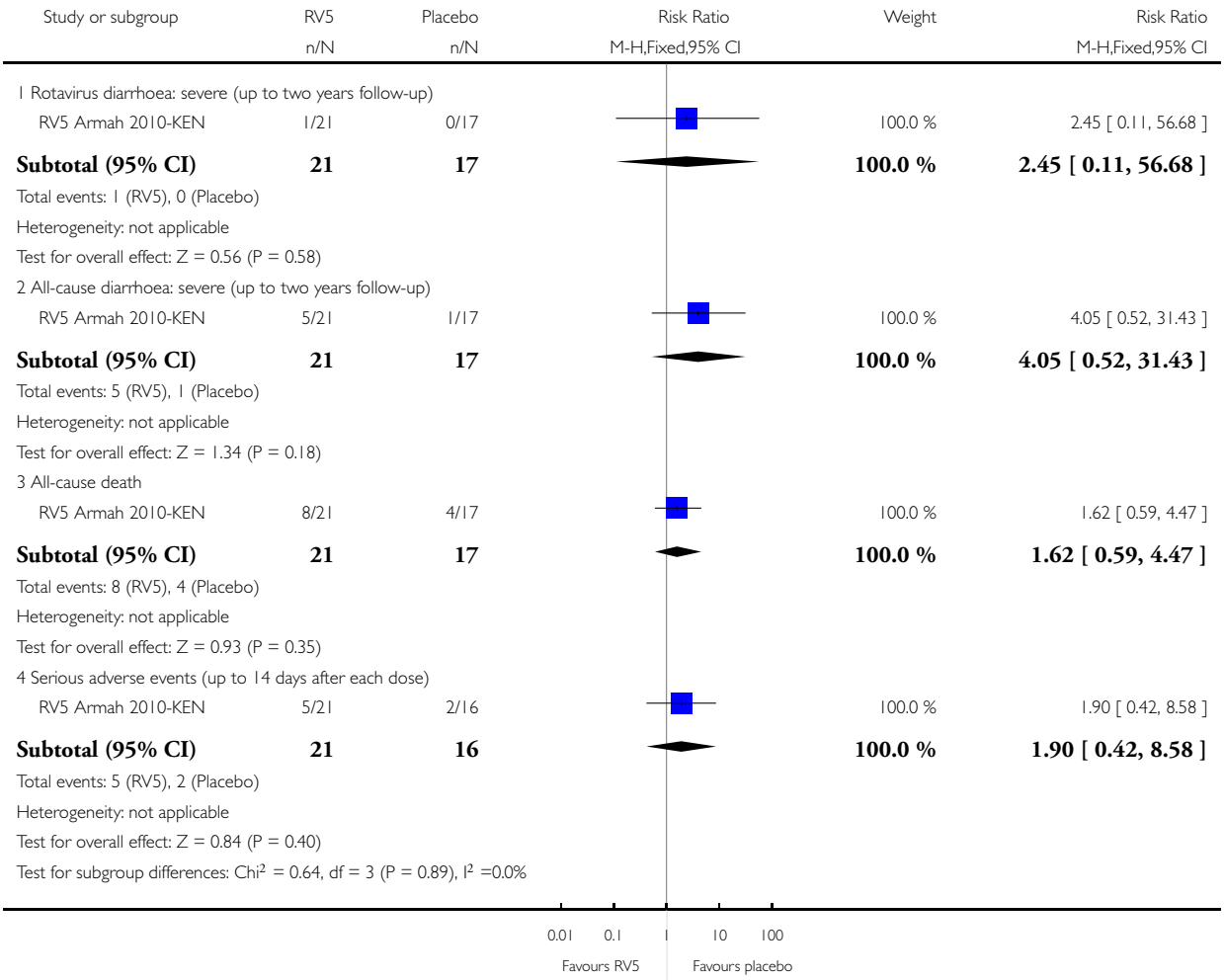


Analysis 2.23. Comparison 2 RV5 versus placebo, Outcome 23 Subgroup analysis: HIV-infected children.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 23 Subgroup analysis: HIV-infected children



Analysis 2.24. Comparison 2 RV5 versus placebo, Outcome 24 Subgroup analysis: rotavirus diarrhoea of any severity in premature babies (1 year follow-up).

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 24 Subgroup analysis: rotavirus diarrhoea of any severity in premature babies (1 year follow-up)

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RV5 Vesikari 2006b-INT	5/84	13/86		100.0 %	0.39 [0.15, 1.06]
Total (95% CI)	**84**	**86**		**100.0 %**	**0.39 [0.15, 1.06]**
Total events: 5 (RV5), 13 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.85 (P = 0.064)					
Test for subgroup differences: Not applicable					

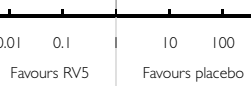
Analysis 2.25. Comparison 2 RV5 versus placebo, Outcome 25 Sensitivity analysis: allocation concealment.

Review: Vaccines for preventing rotavirus diarrhoea: vaccines in use

Comparison: 2 RV5 versus placebo

Outcome: 25 Sensitivity analysis: allocation concealment

Study or subgroup	RV5 n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Rotavirus diarrhoea: severe, up to 2 years follow-up (high-mortality countries)					
RV5 Armah 2010-GHA (1)	26/982	57/989		30.1 %	0.46 [0.29, 0.72]
RV5 Armah 2010-MLI (2)	48/832	58/835		36.8 %	0.83 [0.57, 1.20]
RV5 Zaman 2010-BGD	33/556	56/554		33.2 %	0.59 [0.39, 0.89]
Subtotal (95% CI)	**2370**	**2378**		**100.0 %**	**0.62 [0.44, 0.87]**
Total events: 107 (RV5), 171 (Placebo)					
Heterogeneity: Tau^2 = 0.05; Chi^2 = 4.10, df = 2 (P = 0.13); I^2 =51%					
Test for overall effect: Z = 2.76 (P = 0.0059)					
2 All-cause diarrhoea: severe, up to 1 year follow-up (high-mortality countries)					
RV5 Armah 2010-GHA (3)	49/753	78/737		50.7 %	0.61 [0.44, 0.87]
RV5 Armah 2010-MLI (4)	55/823	56/814		49.3 %	0.97 [0.68, 1.39]
Subtotal (95% CI)	**1576**	**1551**		**100.0 %**	**0.77 [0.49, 1.21]**
Total events: 104 (RV5), 134 (Placebo)					
Heterogeneity: Tau^2 = 0.07; Chi^2 = 3.26, df = 1 (P = 0.07); I^2 =69%					
Test for overall effect: Z = 1.14 (P = 0.25)					
Test for subgroup differences: Chi^2 = 0.57, df = 1 (P = 0.45), I^2 =0.0%					



(1) Total number of participants taken from Tapia et al. 2012, Table 4.

(2) Total number of participants taken from Tapia et al. 2012, Table 4.

(3) Data collected from Tapia et al. 2012, Table 3.

(4) Data collected from Tapia et al. 2012, Table 3.

APPENDICES

Appendix 1. Search methods: detailed search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]	BIOSIS
1	rotavirus	rotavirus	rotavirus	rotavirus	rotavirus	rotavirus
2	diarrhoea	diarrhoea	ROTAVIRUS INFECTIONS	ROTAVIRUS	diarrhoea	diarrhoea
3	diarrhea	diarrhea	1 or 2	1 or 2	diarrhea	diarrhea
4	gastroenteritis	gastroenteritis	diarrhea	diarrhea	gastroenteritis	gastroenteritis
5	2 or 3 or 4	2 or 3 or 4	gastroenteritis	gastroenteritis	2 or 3 or 4	2 or 3 or 4
6	1 and 5	1 and 5	4 or 5	4 or 5	1 and 5	1 and 5

[a] Cochrane Infectious Diseases Group Specialized Register.
[b] Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Lefebvre 2008); upper case: MeSH or EMTREE heading; lower case: free text term.

Appendix 2. Trial type (efficacy or safety) and length of follow-up

Trial	Type: efficacy or safety	Follow-up time
RV1 Anh 2011-PHL	Safety	1 month after last dose
RV1 Anh 2011-VNM	Safety	1 month after last dose
RV1 Bernstein 1998-USA	Safety	1 month
RV1 Bernstein 1999-USA	Efficacy/Safety	2 years
RV1 Dennehy 2005-NA	Safety	10 to 12 months
RV1 GSK[021] 2007-PAN	Safety	1 month after dose 3
RV1 GSK[024] 2008-LA	Efficacy/Safety	Up to age 1 year
RV1 GSK[033] 2007-LA	Safety	1 month
RV1 GSK[041] 2007-KOR	Safety	2 months
RV1 GSK[101555] 2008-PHL	Safety	1 month

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RV1 Kawamura 2010-JPN	Efficacy/Safety	Up to the age of 2 years
RV1 Kerdpanich 2010-THA	Safety	2 months after last dose
RV1 Madhi 2010-AF	Efficacy/Safety	2 years
RV1 Narang 2009-IND	Safety	1 month
RV1 Omenaca 2012-EU	Safety	At least 1 month after dose 2
RV1 Phua 2005-SGP	Efficacy/Safety	Until infant aged 18 months (ie 13 to 15 months)
RV1 Phua 2009-AS	Efficacy/Safety	3 years
RV1 Rivera 2011-DOM	Safety	17 weeks after each dose
RV1 Ruiz-Palac 06-LA/EU	Efficacy/Safety	9 to 10 months
RV1 Salinas 2005-LA	Efficacy/Safety	Up to 2 years
RV1 Steele 2008-ZAF	Safety	Up to 6 months
RV1 Steele 2010a-ZAF	Safety	31 days after each dose, 42 days after the last dose
RV1 Steele 2010b-ZAF	Safety	Up to 6 months
RV1 Vesikari 2004a-FIN	Safety	8 to 30 days after each dose
RV1 Vesikari 2004b-FIN	Efficacy/Safety	1 and 2 years (both reported)
RV1 Vesikari 2007a-EU	Efficacy/Safety	1 and 2 years (plus 3 years in Finland)
RV1 Vesikari 2011-FIN	Safety	2 months
RV1 Ward 2006-USA	Safety	7 days after each vaccination; 3 to 5 weeks after dose 2
RV1 Zaman 2009-BGD	Safety	31 days
RV5 Armah 2010-AF	Efficacy/Safety	Up to 43 days for safety outcomes, up to 21 months for efficacy outcomes
RV5 Block 2007-EU/USA	Efficacy/Safety	42 days for safety/immunogenicity; 1 year for efficacy
RV5 Ciarlet 2009-EU	Safety	42 days
RV5 Clark 2003-USA	Efficacy/Safety	1 year

(*Continued*)

RV5 Clark 2004-USA	Efficacy/Safety	1 year
RV5 Kim 2008-KOR	Safety	42 days
RV5 Merck[009] 2005-USA	Safety	42 days
RV5 NCT00718237 2010-JPN	Efficacy/Safety	25 months
RV5 NCT00953056 2010-CHI	Safety	2 weeks after last dose
RV5 Vesikari 2006a-FIN	Efficacy/Safety	1 to 3 years
RV5 Vesikari 2006b-INT	Efficacy/Safety	43 days for safety; 2 years for efficacy
RV5 Zaman 2010-AS	Efficacy/Safety	Up to 43 days for safety outcomes, up to 2 years for efficacy outcomes

Appendix 3. Efficacy outcome measures by trial

Trial	Rotavirus diarrhoea (any severity)			All-cause diarrhoea		ED visit	Hospitalization (all-cause)	All-cause death	Drop outs
	All	Severe	Hospital	All	Severe				
RV1 Anh 2011-PHL	X			X				X	X
RV1 Anh 2011-VNM	X			X				X	X
RV1 Bernstein 1998-USA									
RV1 Bernstein 1999-USA	X	X	X	X[a]		X[a]		X	
RV1 Dennehy 2005-NA									

(*Continued*)

RV1 GSK[021] 2007-PAN								X	X
RV1 GSK[024] 2008-LA		X			X[a]			X	X
RV1 GSK[033] 2007-LA								X	X
RV1 GSK[041] 2007-KOR	X							X	X
RV1 GSK[10155 2008-PHL	X							X	X
RV1 Kawamura 2010-JPN	X	X	X					X	X
RV1 Kerd-panich 2010-THA	X			X				X	X
RV1 Madhi 2010-AF	X	X	X		X			X	X
RV1 Narang 2009-IND	X							X	X
RV1 Omenaca 2012-EU	X			X					X
RV1 Phua 2009-AS	X[a]	X	X	X[a]	X		X[a]	X	
RV1 Phua 2005-SGP	X	X	X	X	X	X	X	X	X

(*Continued*)

RV1 Rivera 2011-DOM	X			X					X
RV1 Ruiz-Palac 06-LA/EU	X[a]	X	X	X[a]	X		X[a]	X	X[a]
RV1 Salinas 2005-LA	X	X	X	X	X[a]		X[a]	X	
RV1 Steele 2008-ZAF								X	X
RV1 Steele 2010a-ZAF	X			X				X	X
RV1 Steele 2010b-ZAF	X	X						X	X
RV1 Vesikari 2004a-FIN								X[a]	X
RV1 Vesikari 2004b-FIN	X	X	X	X				X	X
RV1 Vesikari 2007a-EU	X	X	X	X[a]	X	X[a]	X[a]		
RV1 Vesikari 2011-FIN	X			X				X	X
RV1 Ward 2006-USA									
RV1 Zaman 2009-BGD	X							X	

(*Continued*)

RV5 Armah 2010-AF	X	X		X	X			X	X
RV5 Block 2007-EU/ USA	X	X						X	X
RV5 Ciarlet 2009-EU								X	
RV5 Clark 2003-USA	X	X[a]							X
RV5 Clark 2004-USA	X	X							X
RV5 Kim 2008-KOR									
RV5 Merck[009] 2005-USA								X	X
RV5 NCT00718 2010-JPN	X	X						X	X
RV5 NCT00953 2010-CHI								X	X
RV5 Vesikari 2006a-FIN	X[a]	X[a]		X	X			X	X
RV5 Vesikari 2006b-INT	X	X	X			X[a]	X[a]	X	X
RV5 Zaman 2010-AS	X	X			X			X	X

[a] Reported as an outcome measure in trial, but no data available for analysis.

Appendix 4. Safety and immunogenicity outcomes measures by trial

Trial	Safety			Immunogenicity	
	Serious AE	Reactogenicity	AE to discontinuation	Vaccine virus shedding	Seroconversion
RV1 Anh 2011-PHL	X	X	X		X
RV1 Anh 2011-VNM	X	X	X		X
RV1 Bernstein 1998-USA	X	X	X	X	X
RV1 Bernstein 1999-USA		X		X	X
RV1 Dennehy 2005-NA	X	X	X	X	X
RV1 GSK[021] 2007-PAN	X	X	X	X	X
RV1 GSK[024] 2008-LA	X		X		X
RV1 GSK[033] 2007-LA	X	X	X	X	X
RV1 GSK[041] 2007-KOR	X	X	X		X
RV1 GSK[101555] 2008-PHL	X	X	X	X	X
RV1 Kawamura 2010-JPN	X	X	X		X
RV1 Kerdpanich 2010-THA	X	X	X	X	X
RV1 Madhi 2010-AF	X				
RV1 Narang 2009-IND	X	X	X		X

(*Continued*)

RV1 Omenaca 2012-EU	X	X			X
RV1 Phua 2005-SGP	X	X	X[a]	X[a]	X
RV1 Phua 2009-AS	X		X		
RV1 Rivera 2011-DOM	X	X			X
RV1 Ruiz-Palac 06-LA/EU	X	X	X		X[a]
RV1 Salinas 2005-LA	X	X		X	X
RV1 Steele 2008-ZAF	X	X	X	X	X
RV1 Steele 2010a-ZAF	X	X[a]		X	X
RV1 Steele 2010b-ZAF	X	X	X	X	X
RV1 Vesikari 2004a-FIN	X	X	X	X	X
RV1 Vesikari 2004b-FIN	X	X	X		X
RV1 Vesikari 2007a-EU	X	X			X
RV1 Vesikari 2011-FIN	X	X	X	X	X
RV1 Ward 2006-USA		X[a]		X	X[a]
RV1 Zaman 2009-BGD	X	X		X	X
RV5 Armah 2010-AF	X	X[a]			X
RV5 Block 2007-EU/USA	X	X	X		X

(*Continued*)

RV5 Ciarlet 2009-EU	X	X	X		X
RV5 Clark 2003-USA	X	X		X	X
RV5 Clark 2004-USA	X[a]	X	X	X	X
RV5 Kim 2008-KOR	X	X[a]	X		X[a]
RV5 Merck[009] 2005-USA	X	X	X		
RV5 NCT00718237 2010-JPN	X[a]	X	X		
RV5 NCT00953056 2010-CHI	X	X[a]	X	X	
RV5 Vesikari 2006a-FIN	X	X			X
RV5 Vesikari 2006b-INT	X	X	X[a]		X
RV5 Zaman 2010-AS	X	X[a]			X[a]

AE: adverse events.
[a]Reported as an outcome measure in trial, but no data available for analysis.

Appendix 5. Trial location

Trial	Year	Location	Sites	Country mortality rate	WHO mortality strata	Region
RV1 Anh 2011-PHL	2007	Philippines	1	Low-mortality	B	Asia
RV1 Anh 2011-VNM	2007	Vietnam	11	Low-mortality	B	Asia

(*Continued*)

RV1 Bernstein 1998-USA	1998	USA	1	Low-mortality	A	North America
RV1 Bernstein 1999-USA	1999	USA	2	Low-mortality	A	North America
RV1 Dennehy 2005-NA	2005	USA and Canada	41	Low-mortality	A	North America
RV1 GSK[021] 2007-PAN	2007	Panama	1	Low-mortality	B	Latin America
RV1 GSK[024] 2008-LA	2008	Argentina, Brazil, Colombia, Dominican Republic, Honduras, and Panama	Multiple sites in each country	Low-mortality	B	Latin America
RV1 GSK[033] 2007-LA	2007	Colombia, Mexico, and Peru	(2 in Colombia, 1 in Mexico, and 4 in Peru)	High-mortality[a]	B, D	Latin America
RV1 GSK[041] 2007-KOR	2007	South Korea	6	Low-mortality	B	Asia
RV1 Narang 2009-IND	2007	India	4	High-mortality	D	Asia
RV1 GSK[101555] 2008-PHL	2008	Philippines	1	Low-mortality	B	Asia
RV1 Kawamura 2010-JPN	2009	Japan	18	Low-mortality	A	Asia
RV1 Kerdpanich 2010-THA	2005	Thailand	2	Low-mortality	B	Asia
RV1 Madhi 2010-AF	2010	South Africa and Malawi	2	High-mortality	E	Africa
RV1 Narang 2009-IND	2009	India	4	High-mortality	D	Asia
RV1 Omenaca 2012-EU	2008	France, Poland, Portugal, and Spain	Multiple sites in each country	Low-mortality	A, B	Europe

(*Continued*)

RV1 Phua 2005-SGP	2005	Singapore	8	Low-mortality	A	Asia
RV1 Phua 2009-AS	2009	Hong Kong, Singapore, and Taiwan	3	Low-mortality	A	Asia
RV1 Rivera 2011-DOM	2008	Dominican Republic	1	Low-mortality	B	Latin America
RV1 Ruiz-Palac 06-LA/EU	2006	Argentina, Brazil, Chile, Colombia, Dominican Republic, Finland, Honduras, Mexico, Nicaragua, Panama, Peru, and Venezuela	Multiple	Low-mortality[b]	A, B, D	Latin America/Europe
RV1 Salinas 2005-LA	2005	Brazil, Mexico, and Venezuela	3	Low-mortality	B	Latin America
RV1 Steele 2008-ZAF	2007	South Africa	1	High-mortality	E	Africa
RV1 Steele 2010a-ZAF	2008	South Africa	5	High-mortality	E	Africa
RV1 Steele 2010b-ZAF	2007	South Africa	7	High-mortality	E	Africa
RV1 Vesikari 2004a-FIN	2004	Finland	2	Low-mortality	A	Europe
RV1 Vesikari 2004b-FIN	2004	Finland	6	Low-mortality	A	Europe
RV1 Vesikari 2007a-EU	2007	Czech Republic, Finland, France, Germany, Italy, and Spain	98	Low-mortality	A	Europe
RV1 Vesikari 2011-FIN	2005	Finland	5	Low-mortality	A	Europe
RV1 Ward 2006-USA	2006	USA	2	Low mortality	A	North America
RV1 Zaman 2009-BGD	2005	Bangladesh	1	High mortality	D	Asia

(*Continued*)

RV5 Armah 2010-AF	2009	Ghana, Kenya, and Mali	3	High-mortality	D, E	Africa
RV5 Block 2007-EU/USA	2007	Finland and USA	30	Low-mortality	A	Europe and North America
RV5 Ciarlet 2009-EU	2008	Austria, Belgium, and Germany	26	Low-mortality	A	Europe
RV5 Clark 2003-USA	2003	USA	19	Low-mortality	A	North America
RV5 Clark 2004-USA	2004	USA	10	Low-mortality	A	North America
RV5 Kim 2008-KOR	2008	South Korea	8	Low-mortality	B	Asia
RV5 Merck[009] 2005-USA	2005	USA	10	Low-mortality	A	North America
RV5 NCT00718237 2010-JPN	2009	Japan	32	Low-mortality	A	Asia
RV5 NCT00953056 2010-CHI	2010	China	Not reported	Low-mortality	B	Asia
RV5 Vesikari 2006a-FIN	2006	Finland	4	Low-mortality	A	Europe
RV5 Vesikari 2006b-INT	2006	Belgium, Costa Rica, Finland, Germany, Guatemala, Italy, Jamaica, Mexico, Puerto Rico, Sweden, Taiwan, and USA	356	Low-mortality[b]	A, B, D	Asia, Caribbean, Europe, Latin America, North America
RV5 Zaman 2010-AS	2009	Bangladesh and Vietnam	Multiple	High-mortality[a]	B, D	Asia

[a] This study was conducted mainly in high-mortality countries, but also in low-mortality countries.
[b] This study was conducted mainly in low-mortality countries, but also in high-mortality countries.

Appendix 6. Vaccine schedules

Trial	No. doses	Time between doses (weeks)	No. arms: vaccine/ placebo	Infant vaccination status	Note
RV1 Anh 2011-PHL	2	4 or 8	2/1	Commercially available diphtheria, tetanus, whole-cell pertussis (DTPw), hepatitis B (HBV) and oral poliovirus (OPV) vaccines were administered concomitantly with the study vaccine/placebo as part of the routine Expanded Programme of Immunization (EPI) in the Philippines	Compares different schedules: (1) vaccine dose at month 1 and 2, and placebo at day 0; and (2) vaccine dose at day 0 and month 2, and placebo at month 1
RV1 Anh 2011-VNM	2	4 or 8	2/1	Commercially available diphtheria, tetanus, whole-cell pertussis (DTPw), hepatitis B (HBV) and oral poliovirus (OPV) vaccines were administered concomitantly with the study vaccine/placebo as part of the routine Expanded Programme of Immunization (EPI) in Vietnam	Compares different schedules: (1) vaccine dose at day 0 and month 1, and placebo at month 2; and (2) vaccine dose at day 0 and month 2, and placebo at month 1
RV1 Bernstein 1998-USA	2	6 to 10	1/1	Rotavirus vaccine was separated from all other infant vaccines by at least 2 weeks	-
RV1 Bernstein 1999-USA	2	6 to 10	1/1	Other vaccines separated from the trial vaccines by at least 2 weeks	-
RV1 Dennehy 2005-NA	2	7	2/1	Vaccine or placebo given concomitantly with diphtheria-tetanus-acellular per-	2 different PFUs compared

(*Continued*)

				tussis, inactivated poliovirus, *H. influenzae* type b, and *S. pneumoniae* conjugate vaccines for participants in USA or with a diphtheria-tetanus-acellular pertussis/inactivated poliovirus/*H. influenza* type b combination vaccine for participants in Canada "Routine hepatitis B vaccinations were administered according to local practice."	
RV1 GSK[021] 2007-PAN	3	8	2/2	Use of other vaccines not mentioned	Licensed formulation versus modified formulation
RV1 GSK[024] 2008-LA	2	4 or 8	1/1	All participants received routine infant vaccinations (Hepatitis B vaccine), diphtheria-tetanus-acellular pertussis, poliovirus, and *H. influenzae* type b) according to Expanded Program of Immunization (EPI) recommendations in each country First 2 doses of routine EPI vaccinations were co-administered with the RV1 vaccine or placebo doses; the third routine EPI vaccination was administered 1 to 2 months later according to the national plan of immunization in each country	-

(*Continued*)

RV1 GSK[033] 2007-LA	2	8	3/1	Use of other vaccines not mentioned	3 'Lots' of RV1 vaccine compared
RV1 GSK[041] 2007-KOR	2	8	1/1	*H. influenzae* type b vaccine administered concomitantly along with the 2 doses of vaccine/placebo and at 2 months after dose 2; other routine childhood vaccines were to be given at least 14 days before trial vaccine/placebo	-
RV1 GSK[101555] 2008-PHL	2	8	2/2	No mention of whether infants received other vaccines	Data from the lyophilized formulation, which is not yet approved or marketed, are not reported
RV1 Kawamura 2010-JPN	2	4	1/1	Combined diphtheria and tetanus toxoids and acellular pertussis (DTPa) and Hepatitis B (HBV) vaccines were allowed to be co-administered along with RV1 vaccine/placebo	-
RV1 Kerdpanich 2010-THA	2	8	3/2	Diphtheria toxoid, tetanus toxoid, acellular pertussis, inactivated polio and *H. influenzae* type b combination vaccine (*Infanrix* ^{TM} -IPV/Hib) at two and four months of age and diphtheria toxoid, tetanus toxoid, acellular pertussis, hepatitis B, inactivated polio and *H. influenzae* type b combination vaccine (*Infanrix hexa*^{TM}) at six months of age	Compares: regular vaccine reconstituted in buffer; vaccine reconstituted in water; vaccine stored above recommended temperature; placebo reconstituted in water; placebo reconstituted in buffer

(*Continued*)

RV1 Madhi 2010-AF	2 or 3	5 to 10	2/1	All participants received routine infant vaccinations according to Expanded Program on Immunization (EPI) recommendations	-
RV1 Narang 2009-IND	2	8	1/1	Routine vaccinations (diphtheria-tetanus-whole cell pertussis-hepatitis b, *H. influenzae* type b, and oral poliovirus vaccine) were administered at 6, 10, and 14 weeks of age (given with a 2-week separation from the first and subsequent dose of the RV1 vaccine or placebo)	-
RV1 Omenaca 2012-EU	2	4 or 8	1/1	All participants received routine infant vaccinations in accordance with the local National Plan of Immunisation schedule in each of the respective participating countries	-
RV1 Phua 2005-SGP	2	4	3/1	Hepatitis B vaccine, diphtheria-tetanus-acellular pertussis, poliovirus, and *H. influenzae* type b co-administered with interventions	3 different PFUs compared
RV1 Phua 2009-AS	2	6 to 10	1/1	Infants received other routine paediatric immunizations (combined diphtheria toxoid-tetanus toxoid-acellular pertussis [DTPa] - inactivated poliovirus [IPV] and *H. influen-*	-

(*Continued*)

				zae type B [Hib] vaccine and hepatitis B vaccine [HBV]) during the study period according to local schedules. Almost all infants received Bacille Calmette-Guérin (BCG) dose at birth. If oral polio vaccine (OPV) was given as part of the routine schedule in the participating countries, a time interval of 2 weeks was observed between the OPV doses and RIX4414 vaccine/placebo doses	
RV1 Rivera 2011-DOM	2	7	1/1	All infants received three doses of combined diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliovirus and *H. influenzae* vaccine.	One complimentary dose of RV1 was administered to all infants enrolled in this study (both study groups) who were aged less than 6 months at Visit 3 (Week 13) as a benefit to the placebo group for participation in the study
RV1 Ruiz-Palac 06-LA/EU	2	4 or 8	1/1	Routine immunizations according to local regulations; oral poliovirus vaccination at least 2 weeks before or after rotavirus vaccine	-
RV1 Salinas 2005-LA	2	8	3/1	Oral polio vaccine given after 2 weeks, not together with RV1	3 different PFUs compared Main publication did not report that the trial included 2 subsets: 2 doses of human rotavirus or placebo sub-

(*Continued*)

					set: these participants received 2 oral doses of RV1 vaccine or placebo according to a 0, 2 months schedule, and routine vaccinations (DTPw- Hepatitis B vaccine (HBV) + Hib vaccine) at a 0, 2, and 4 months schedule 3 doses of RV1 or placebo subset: these participants received 3 oral doses of RV1 vaccine or placebo, and routine vaccinations (DTPw-HBV + Hib vaccine) concomitantly with each dose of human rotavirus vaccine and placebo at a 0, 2, and 4 months schedule
RV1 Steele 2008-ZAF	2	4	3/1	RV1 plus (1) oral polio vaccine (OPV) + diphtheria-tetanus-acellular pertussis/*H. influenzae* type b (DTPA/HIB) vaccine; (2) OPV placebo + diphtheria-tetanus-acellular pertussis inactivated polio-*H. influenzae* type b (DTPA-IPV/HIB) vaccine; or (3) OPV + DTPA/HIB vaccine	Compares different co-administration combinations (see previous column)
RV1 Steele 2010a-ZAF	3	4	1/1	RV1 vaccine was concomitantly administered with 3 doses of combined diphtheria, tetanus and whole-cell pertussis, hepatitis B, and *H. influenzae* type b vaccine (Tritanrix-	For infants who developed clinical symptoms of HIV (WHO stages III or IV disease) anytime after enrolment, access to antiretroviral therapy (cotrimox-

(*Continued*)

				HepBHib) and OPV (PolioSabin)	azole) according to the South African national guidelines was facilitated. Infants who needed treatment were referred to antiretroviral therapy centres by the investigators
RV1 Steele 2010b-ZAF	2 or 3	4	2/1	Infants received routine vaccinations according to the local EPI schedule in South Africa. Bacille Calmette-Guerin and OPV vaccinations were given at birth; all other routine vaccinations (including diphtheria-tetanus toxoids-whole cell pertussis, hepatitis B, *H. influenzae* type b, and OPV) were administered concomitantly with the study vaccine	Compares number of doses (2 or 3)
RV1 Vesikari 2004a-FIN	2	8	3/1	Infant routine vaccinations were separated from the study vaccines by 2 weeks	3 different PFUs compared
RV1 Vesikari 2004b-FIN	2	8	1/1	Infant routine vaccinations (diphtheria tetanus toxoids-pertussis, *H. influenzae* type b, and inactivated poliovirus vaccines) were separated from the study vaccines by at least 2 weeks	-
RV1 Vesikari 2007a-EU	2	4 or 8	1/1	Concomitant vaccines included 7 valent pneumococcal polysaccharide conjugate vaccine (Prevenar) and meningococ-	-

(*Continued*)

				cal group c conjugate vaccine (Meningitec); Hepatitis B vaccine, diphtheria-tetanus-acellular pertussis, polio virus, and *H. influenzae* type b vaccines were co-administered	
RV1 Vesikari 2011-FIN	2	4	2/2	Routine childhood vaccinations were allowed according to local practice, but at least 14 days apart from each dose of study vaccine	Compares liquid and lyophilized vaccine formulations
RV1 Ward 2006-USA	2	4	2/1	Not specified	2 different PFUs compared
RV1 Zaman 2009-BGD	2	-	2/2	All children in the study received the standard EPI vaccines starting at 6 weeks of age. Oral polio vaccine (OPV) co-administered in trial: either concomitantly with RV1 or 15 days before RV1	Compared RV1 plus oral polio vaccine with RV1 alone
RV5 Armah 2010-AF	3	4	1/1	All children in the study received the standard EPI vaccines (including oral poliovirus vaccine) starting at 6 weeks of age	-
RV5 Block 2007-EU/USA	3	4 to 10	1/1	Use of oral poliovirus vaccine during the course of the study or within 42 days before first dose of vaccine/placebo was an exclusion criterion; administration of other vaccines permitted	-

(*Continued*)

RV5 Ciarlet 2009-EU	3	4 to 6	1/1	Hepatitis B vaccine, diphtheria-tetanus-acellular pertussis, polio virus, and *H. influenzae* type b co-administered	-
RV5 Clark 2003-USA	3	6 to 8	1/1	Children that had recently received oral polio vaccine were excluded from the study	Breastfed; infants in the vaccine control group (Group 1) received the reassortants as administered in previous studies within 30 min of feeding Enfamil formula (30 ml) or Mylanta Double Strength (0.5 ml/kg). Infants in a corresponding placebo group (Group 2) were pre-fed as in Group 1
RV5 Clark 2004-USA	3	6 to 8	1/1	Receipt of any other vaccines within 14 days was not allowed	-
RV5 Kim 2008-KOR	3	4 to 10	1/1	Infants excluded if they had or were to receive oral poliovirus vaccine at any time during the study or in the 42 days before the first dose; concomitant administration of other licensed vaccines and breastfeeding was not restricted	-
RV5 Merck[009] 2005-USA	3	4 to 10	1/1	Infants were excluded if they had or were to receive oral poliovirus vaccine at any time during the study or in the 42 days before the first dose; concomitant administration of other licensed vaccines	-

(*Continued*)

				and breastfeeding was not reported	
RV5 NCT00718237 2010-JPN	3	4 to 10	1/1	No information about use of other vaccines	-
RV5 NCT00953056 2010-CHI	3	4 to 10	1/1	Other live vaccines 14 days before or after study vaccine were not allowed	-
RV5 Vesikari 2006a-FIN	3	4 to 8	3/1	Licensed vaccines could be administered throughout the study, but were not given on the same day as study vaccine; inactivated poliovirus vaccine was exclusively used in Finland at the time of the study	Compares different RV5 components: G1-4, P1A; G1-4; and P1A
RV5 Vesikari 2006b-INT	3	4 to 10	1/1	Administration of other licensed childhood vaccines and breastfeeding were not restricted; for a subset of subjects in the USA (U.A. concomitant use cohort), Merck also provided the licensed paediatric vaccines that were administered concomitantly (same day) with RV5 or placebo, which included Comvax, Infanrix, Ipol, and Prevnar	-
RV5 Zaman 2010-AS	3	4	1/1	All children in the study received the standard EPI vaccines (including oral poliovirus vaccine) starting at 6 weeks of age	-

H. influenzae: *Haemophilus influenzae*; PFU: plaque-forming unit.

Appendix 7. Methods to collect adverse event data

Trial	Passive or active
RV1 Anh 2011-PHL	Not reported
RV1 Anh 2011-VNM	Not reported
RV1 Bernstein 1998-USA	Passive
RV1 Bernstein 1999-USA	Passive and active
RV1 Dennehy 2005-NA	Passive and active
RV1 GSK[021] 2007-PAN	Not reported
RV1 GSK[024] 2008-LA	Not reported
RV1 GSK[033] 2007-LA	Not reported
RV1 GSK[041] 2007-KOR	Not reported
RV1 GSK[101555] 2008-PHL	Not reported
RV1 Kawamura 2010-JPN	Not reported
RV1 Kerdpanich 2010-THA	Passive
RV1 Madhi 2010-AF	Active
RV1 Narang 2009-IND	Passive
RV1 Omenaca 2012-EU	Not reported
RV1 Phua 2005-SGP	Passive
RV1 Phua 2009-AS	Passive
RV1 Rivera 2011-DOM	Passive
RV1 Ruiz-Palac 06-LA/EU	Active
RV1 Salinas 2005-LA	Passive
RV1 Steele 2008-ZAF	Not reported
RV1 Steele 2010a-ZAF	Active and passive
RV1 Steele 2010b-ZAF	Not reported

(*Continued*)

RV1 Vesikari 2004a-FIN	Passive
RV1 Vesikari 2004b-FIN	Passive
RV1 Vesikari 2007a-EU	Passive and active
RV1 Vesikari 2011-FIN	Passive
RV1 Ward 2006-USA	Not reported
RV1 Zaman 2009-BGD	Passive and active
RV5 Armah 2010-AF	Active
RV5 Block 2007-EU/USA	Passive and active
RV5 Ciarlet 2009-EU	Passive and active
RV5 Clark 2003-USA	Passive and active
RV5 Clark 2004-USA	Passive and active
RV5 Kim 2008-KOR	Passive
RV5 Merck[009] 2005-USA	Not reported
RV5 NCT00718237 2010-JPN	Passive
RV5 NCT00953056 2010-CHI	Not reported
RV5 Vesikari 2006a-FIN	Passive and active
RV5 Vesikari 2006b-INT	Active
RV5 Zaman 2010-AS	Active and passive

Appendix 8. Ongoing studies: vaccine and location

Trial	Rotavirus vaccine	Location	
		Region	Country
Other ACTRN12610000525088	RV3-BB	Oceania	Australia

(*Continued*)

Other ACTRN12611001212943	RV3-BB	Oceania	New Zealand
Other CTRI-091-000102	ORV 116E	Asia	India
Other CTRI-091-003064	RotaVac	Asia	India
Other CTRI2009-091-000821	RotaVac	Asia	India
Other NCT00981669	Brazilian Rotavirus vaccine	South America	Brazil
Other NCT01061658	BRV-TV	Asia	India
Other NCT01266850	RV1 and RV5	North America	US
Other NCT01305109	ORV 116E	Asia	India
Other NCT01571505	Unspecified rotavirus vaccine	Asia	India
RV1 ISRCTN37373664	RV1	Africa	South Africa
RV1 ISRCTN86632774	RV1	Africa	South Africa
RV1 NCT00134732	RV1	Asia	Republic of Korea
RV1 NCT00158756	RV1	Europe	Moscow, Russian Federation
RV1 NCT00289172	RV1	Asia	India
RV1 NCT00383903	RV1	Africa	South Africa
RV1 NCT00420316	RV1	Europe	Finland
RV1 NCT00425737	RV1	Europe	Finland
RV1 NCT00429481	RV1	Asia	Singapore
RV1 NCT01171963	RV1	Asia	China
RV1 NCT01199874	RV1	Asia	Pakistan
RV1 NCT01375647	RV1	Asia	Bangladesh
RV1 NCT01575197	RV1	Africa	Ghana
RV1 Tatochenko 2008	RV1	Not reported	Not reported
RV5 NCT00880698	RV5	Africa	Botswana

Appendix 9. Deaths[a]: from published trials and from communication with trial authors

Vaccine	Trial	No. of deaths				Cause of death
		Vaccine	Placebo	Unclear	Total	
RV1	RV1 Anh 2011-PHL	1	0	0	1	*Salmonella* gastroenteritis
	RV1 Anh 2011-VNM	0	0	0	0	-
	RV1 Bernstein 1998-USA	0	0	0	0	-
	RV1 Bernstein 1999-USA	0	0	1 (1)	1	Pneumococcal sepsis
	RV1 GSK[021] 2007-PAN	0	0	0	0	-
	RV1 GSK[024] 2008-LA	10	2	0	12	Meningitis bacterial (1 vaccine, 1 placebo), pneumonia (3 vaccine), aortic valve stenosis (1 vaccine), bronchiolitis (1 vaccine), dengue fever (1 vaccine), endocarditis bacterial (1 vaccine), intussusception (1 vaccine), multi-organ failure (1 placebo), respiratory failure (1 vaccine), sepsis (2 vaccine)
	RV1 GSK[033] 2007-LA	3	0	0	3	Gastroenteritis (1 vaccine), bronchopneumonia (1 vaccine), aspiration (1 vaccine)
	RV1 GSK[041] 2007-KOR	0	0	0	2	Not reported
	RV1 GSK[101555] 2008-PHL	0	0	0	0	-
	RV1 Kawamura 2010-JPN	0	0	0	0	-
	RV1 Kerdpanich 2010-THA	0	0	0	0	-
	RV1 Madhi 2010-AF	83	43	0	126	Reasons not stated
	RV1 Narang 2009-IND	0	0	0	0	-

(*Continued*)

	RV1 Phua 2005-SGP	3	0	0	3	Leukaemia (1 vaccine); accident induced subarachnoid haemorrhage (1 vaccine); cardiorespiratory failure after acute viral pneumonitis (1 vaccine)
	RV1 Phua 2009-AS	1	3	0	4	Aspiration and metabolic disorder, adenoviral pneumonia, interstitial pneumonia, and sudden infant death syndrome (not stated which group)
	RV1 Rivera 2011-DOM	0	0	0	0	-
	RV1 Ruiz-Palac 06-LA/EU	56	43	0	99	Diarrhoea (4 vaccine, 2 placebo); pneumonia (16 vaccine, 6 placebo); other causes not mentioned
	RV1 Salinas 2005-LA	2	1	0	3	Generalised visceral congestion (1 placebo); sepsis (1 vaccine); automobile accident (1 vaccine)
	RV1 Steele 2008-ZAF	3	5	0	8	Bronchopneumonia (1 placebo), pneumonia (2 vaccine, 2 placebo), hepatic steatosis (1 placebo), brain oedema (1 vaccine, 1 placebo)
	RV1 Steele 2010a-ZAF	6	9	0	15	Bronchopneumonia, sepsis, and gastroenteritis were the most common causes
	RV1 Steele 2010b-ZAF	3	0	0	3	Bronchopneumonia and gastroenteritis (3 vaccine)
	RV1 Vesikari 2004b-FIN	0	0	0	0	-
	RV1 Vesikari 2007a-EU	0	0	0	0	-
	RV1 Vesikari 2011-FIN	0	0	0	0	-
	RV1 Zaman 2009-BGD	1	0	0	1	
RV5	RV5 Armah 2010-AF	76	82	0	158	Gastroenteritis (20 vaccine, 16 placebo); 11 deaths occurred in identified HIV infected participants in Kenya; sudden infant death syndrome (1 placebo); other causes not mentioned
	RV5 Block 2007-EU/USA	1	0	0	1	Sudden infant death syndrome (1 vaccine)
	RV5 Ciarlet 2009-EU	0	0	0	0	-

(*Continued*)

	RV5 Merck[009] 2005-USA	0	0	0	0	-
	RV5 NCT00718237 2010-JPN	0	0	0	0	-
	RV5 NCT00953056 2010-CHI	0	0	0	0	-
	RV5 Vesikari 2006a-FIN	0	0	0	0	-
	RV5 Vesikari 2006b-INT	24	20	0	44	Sudden infant death syndrome (7 vaccine and 7 placebo), other causes not mentioned
	RV5 Zaman 2010-AS	3	4	0	7	Not all causes reported, most common causes were drowning and sepsis

[a] Numbers in brackets are the number of deaths reported by the trial authors following personal communication with them, ie they are not in the published trial reports.

WHAT'S NEW

Last assessed as up-to-date: 10 May 2012.

Date	Event	Description
10 May 2012	New search has been performed	No new trials were identified from the updated May 2012 search
10 May 2012	New citation required but conclusions have not changed	Review updated to incorporate different country mortality strata and outcomes changed to reflect the different rotavirus vaccines' efficacy and safety in countries with different mortality rates

HISTORY

Protocol first published: Issue 4, 2000

Review first published: Issue 5, 2010

Date	Event	Description
8 January 2012	New search has been performed	Review updated to include nine trials identified in a new literature search, which was conducted in October 2011 (MEDLINE via PubMed) and June 2011 (other databases)
11 November 2011	New citation required but conclusions have not changed	Hanna Bergman and Sukkrti Nagpal joined the author team.
10 May 2010	Amended	Minor typographical errors corrected.
2 February 2010	New citation required and conclusions have changed	A new search on 2 February 2010 identified 9 new potentially relevant studies. We independently assessed these studies and incorporated data from the eligible trials into the review
21 July 2009	New search has been performed	The original rotavirus vaccines review (Soares-Weiser 2004) was split into two reviews: rotavirus vaccines in use (this review); and other rotavirus vaccines, including those no longer in use or in development (Soares-Weiser 2004). This involved a new search, revised inclusion criteria, updated review methods. All data from those trials also included in the original review were re-extracted. New authors joined the review team for this review

CONTRIBUTIONS OF AUTHORS

Irit Ben-Aharon: extracted and inputted data, including risk of bias assessment, and helped write the background and effects of interventions.

Hanna Bergman: created summary of findings tables, extracted, inputted and analysed data, including risk of bias assessment, updated the review text for this update.

Nigel Cunliffe: provided guidance on inclusion criteria, review structure, and content; and commented on review drafts.

Elad Goldberg: designed data forms and analysed data.

Harriet MacLehose: updated review methods, assisted with data form design and data management, resolved data extraction queries, and, with Karla Soares-Weiser, took the lead with writing the review.

Sukrti Nagpal: updated screening and extracted data, including risk of bias assessment.

Femi Pitan: piloted data extraction form, provided guidance on inclusion criteria, and helped write the background.

Karla Soares-Weiser: updated review methods, designed data forms, took the lead in extracting and analysing data, including risk of bias assessment; and, with Harriet MacLehose, took the lead in writing the review.

DECLARATIONS OF INTEREST

Irit Ben-Aharon: none known.

Hanna Bergman: works for Enhance Reviews. Enhance Reviews Ltd is a private company that performs systematic reviews of the literature.

Nigel Cunliffe: Principal Investigator on a clinical trial of RV1, has received research grant support and lecture fees from GlaxoSmithKline Biologicals and Sanofi Pasteur MSD.

Elad Goldberg: none known.

Harriet MacLehose: none known.

Sukrti Nagpal: none known.

Femi Pitan: none known.

Karla Soares-Weiser: has received payment in the past (not for the current update) to conduct this review from the DFID UK via the Effective Health Care Research Programme Consortium (see 'Sources of support'). Enhance Reviews Ltd. is a private company that performs systematic reviews of the literature.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Department for International Development (DFID), UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This is an update of the original rotavirus vaccines review (Soares-Weiser 2004). This review concerns vaccines in use.

INDEX TERMS

Medical Subject Headings (MeSH)

Diarrhea [*prevention & control; virology]; Diarrhea, Infantile [*prevention & control; virology]; Infant, Newborn; Randomized Controlled Trials as Topic; Rotavirus Infections [*prevention & control]; Rotavirus Vaccines [*therapeutic use]; Vaccines, Attenuated [therapeutic use]

MeSH check words

Humans; Infant